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Co-plnt McKnight Exhibit 1
C-2017-2621057
4/10/18 Phila PUC

Dr. Alexia McKnight
258 Heyburn Rd.
Chadds Ford, PA 19317
610-459-1031

September 27, 2016

PERSONAL and CONFIDENTIAL

Mr. Craig Adams
Executive Vice President, Exelon
President and CEO, PECO
2301 Market Street
Philadelphia, PA 19103

Dear Mr. Adams,

This letter relates my experience with a recent upgrade to the AMI wireless smart meter. I am writing to bring a problem to your attention and am requesting an accommodation.

I recognize these are controversial devices that are the object of much scrutiny among scientists, clinicians, and attorneys. While some suggest that the devices are safe, there are many anecdotes of health deteriorations following deployment of these meters. Furthermore, research on non-thermal biologic effects of electromagnetic fields suggests a select subgroup of the population that experiences negative health effects following exposure to wireless and other electromagnetic radiation. My own case, described below, shows that I am a member of this subpopulation.

On November 30, 2015 PECO upgraded the electric meter on our house to a wireless AMI smart meter. The following symptoms I had been experiencing were immediately and markedly exacerbated:

- inability to sleep
- significant headaches
- failing memory
- impaired concentration
- vitreous detachment (light flashes followed by eye 'floaters')
- mood alterations
- irritability
- unusual leg pains
- ringing and pressure pain in the ears

While these symptoms are nonspecific, the severity became impairing. To obtain any reprieve from them, I had to depart the house at night for the first few weeks in December and camp out in the yard in order to sleep. The associated timing of the AMI deployment and the exacerbation of these symptoms was instructive, and after much research and several expert consultations, my husband and I measured and removed most of the sources of radiofrequency in the house. This included turning off all wifi routers,

entertainment electronics and remote controls, cell phones, wireless printers, bluetooth and wifi-enabled computers, and smart watches. Most other sources of biologically irritating electromagnetic fields (dimmer switches, fluorescent lights, some LEDs, wiring errors) were also identified and eliminated or fixed. We learned that if we opened the circuit breakers to de-power the upstairs bedrooms, I was able to sleep in the house again.

Many of my symptoms clearly improved. Nonetheless, my headaches persisted and I developed cardiac palpitations. These arrhythmias progressed so much that I made an appointment to see a cardiologist.

Around this time, we also identified a stray voltage grounding error found to be caused from the PECO source neutral. These electrical problems were brought to the attention of PECO on March 21, 2016. PECO emergency and power quality crews subsequently both confirmed the neutral failure, and have promised to fix this, however after 6 months these fixes are still pending.

On May 24, 2016, PECO power quality personal replaced the AMI meter with a plate while investigating the stray voltage problem. A few weeks after the AMI meter was off the house, my arrhythmias drastically improved. Fortuitously, the plate remained on the house as PECO continued to investigate the stray voltage problem. About one month after the AMI meter was removed, the arrhythmias had completely vanished and I no longer needed cardiac attention. My headaches also disappeared entirely.

I was feeling nearly normal again, living and working in the house without symptoms. However, if visitors came into the house with a cell phone that had not yet been turned off or placed into 'airplane' mode, I would feel a pain as if a vise were pressed into my temples. Traveling also became progressively very difficult. Leaving the house, symptoms would frequently return. I am now hypersensitive to the point that this illness has become a disability. I can no longer attend church, go to restaurants or shops with wifi, or visit other public or private gatherings without significant physical discomfort, cognitive and mood impairment, and sleep disturbances. Fortunately, my refuge was my home where I live and work.

Then, around the middle of September, my headaches returned, I began having sleeping problems, and some minor cardiac arrhythmias returned. Just recently, on September 21, 2016, I noticed PECO had replaced the plate with the AMI smart meter. I do not know exactly on what day this occurred, but the house has been notably uncomfortable again for the past few weeks. Thus, while the mechanisms by which the meter interacts with this house and my physical health are not clear, it is clear that I am simply unable to tolerate this meter.

I am a veterinary radiologist, running a teleradiology practice from home. My husband was an electrical engineer before becoming a physician, specializing in both internal medicine and medical informatics. We are both professionals, with combined backgrounds is science, academia, medicine, industry, and the biologic effects of

radiation. Given that electrical hypersensitivity syndrome (EHS) is not yet widely accepted in the medical community, my husband was initially skeptical that electromagnetic fields were a cause of my symptoms. However, our personal experience has provided the evidence that convinces us of the authentic existence of this condition and the unfortunate need for total avoidance. In medicine, there is no better evidence of causality for an individual patient than an "N of 1" medical experiment when a patient acts as his/her own control. In this case, when the meter was introduced, my symptoms became worse. When the meter was removed, my symptoms improved. Finally, when the meter returned, my symptoms returned. Ironically, and unfortunately for me, this history formed exactly this kind of N of 1 experiment.

My husband and I would like to meet and discuss this problem and acceptable accommodations, with yourself or another executive authorized to make decisions. I simply ask for clean power to this house and an electric meter that does not make me ill.

As a proposed solution, I acquired a calibrated analog meter and left it outside by the electrical box. I noticed this meter was no longer there when I saw the new AMI meter on the house. I also request that analog meter be returned, if it is found not to be acceptable. Perhaps PECO needed to calibrate it themselves and/or examine it for safety?

Please forward this letter to those handing customer accommodations under the Americans with Disabilities Act and under Section 504 of the Rehabilitation Act of 1973. Thank you for your prompt attention to this matter. And thank you for your confidentiality given the personal health nature of this letter.

Sincerely yours,

Alexia McKnight, DVM, DACVR
PECO Account No: 89900-01209

CC: Dr. Umer Saleem, MD
CC: Mr. Christopher Crane

Complaint McKnight Exhibit 2
C-2017-2621057
4/10/18 Phila PK

Peter J. Prociuk, MD
Board Certification In Internal Medicine
Classical Homeopathy
www.drpeterprociuk.com

March 8, 2017

Tracy A. Hannan
Assistant General Counsel
Exelon Corporation
10 S. Dearborn St., 49th Floor
Chicago, Illinois 60603

Re: Alexia McKnight DOB 2/15/1971
EMF Hypersensitivity Syndrome
Medical Necessity For Analogue Electric Meter

Dear Tracy Hannan,

Alexia McKnight has been my patient since 4/27/2010. Her primary diagnosis, made within the last year, is EMF Hypersensitivity Syndrome. Accordingly, it is a medical necessity for EMF to be at an absolute minimum in her home environment and to meet this goal a smart meter on or near her house is a medical contraindication. Her history is as follows:

About 10 years ago she noticed significant pain on the side of my head if a cell phone was held to her ear. Pain was also felt in her hand if holding a cell phone, and similarly would feel an uncomfortable tingle up the arm when using an iPad. She would also experience an occasional pain deep in her ears at home and sometimes while driving on Interstate 95. This was the same pain experienced now associated with strong cellular signals and wifi exposure. She would also experience signifiant pain in her ears/head with some headsets, including the Bose noise canceling headsets.

Starting 6 years ago her health began to progressively deteriorate in spite of a meticulously healthy lifestyle. She was increasingly more fatigued with bouts of severe fatigue along occasional depression and irritablity that was uncharacteristic. Her skin and eyes lacked luster despite excellent nutrition and she gained weight with no change in diet or exercise routine. She had trouble reading and comprehending, particularly her own dictations made in the course of

her profession as an equine radiologist with a speciality in MRI imaging. It is important to note that she works in a home office.

Her short term memory started to fail and her vision was compromised by progressively more floaters. Her visual acuity also worsened along with more frequent headaches. Her ability to concentrate on her cases while working on the computer worsened, she became progressively agitated and the quality of her sleep deteriorated. This brings us to 2014 at which time there was no obvious explanation for this change in her health.

All of this was markedly and suddenly exacerbated when PECO upgraded the electric meter to an AMI meter on November 30, 2015. She was completely unable to sleep, headaches were nearly constant and she had a miserable 'out of sorts' feeling. Her memory starting failing so badly she was having trouble remembering if a red light or a green light meant 'go' at a stoplight. A few sentences into a conversation she would stop and have no idea what she said. She could barely perform at her job. All this started creating significant anxiety and cardiac arrhythmias started.

She realized that sleep was possible outside in the yard which she did using the family sailboat for shelter. This seemingly extreme measure has to be appreciated in the context of being a high functioning professional with no prior significant medical or psychiatric history.

Being scientifically oriented and strongly proactive in nature, she undertook serious research into EMF and its biologic/clinical effects. Upon discovering a significant body of scientific evidence and clinical reports confirming EMF Hypersensitivity Syndrome her husband, a board certified internist, and she took numerous measures to reduce the electromagnetic fields in the house.

They turned off both wifi routers in the house, disabled all wifi devices, disabled or discarded wireless printers, wireless entertainment devices, wireless watches. They removed all the LED and fluorescent lights with incandescent bulbs and replaced all dimmer switches with standard light switches. They measured very strong electrical fields in the house, particularly the bedrooms, and started sleeping with the circuit breakers off to the upstairs bedrooms at night.
All of this helped significantly and she was able to sleep in the house again.
However her headaches and cardiac arrhythmia persisted.

In March 2016 they hired an EMF consultant who pointed out additional stray voltage on the house electrical grounding system and some wiring errors. PECO emergency and power quality crews came out and in the process of investigating the problem removed the smart meter on May 24, 2016. Her cardiac arrythmia started to improve in about one week, was significantly better in 2 weeks, and nearly resolved in 1 month. Her headaches also resolved.

She was referred to Dr Umer Saleem, a board certified cardiologist on 6/20/2016 to rule out any other cardiac pathology. He found her symptoms correlated with premature atrial and ventricular contractions and based on the history concurred that EMF exposure was the likely cause. His subspeciality is in the field of cardiac arrthymias.

She felt near normal during the summer of 2016. Her headaches, sleep problems, cardiac arrhythmia, irritability, concentration and depressive moods returned in September 2016. After a few weeks she discovered the AMI smart meter had been placed back on the house 9/21/2016. PECO power quality removed the meter the second time on November 1, 2016 and again her symptoms improved.

Although this hypersensitivity syndrome has not been formally recognized and has neither formal dignostic criteria or an ICD 10 code, it is scientifically recognized that EMF can produce significant biologic injury that correlates with Alexia's symptoms. The clear pattern of being progressively symptomatic in an EMF environment and improving with a significant reduction in EMF twice in a row is consistent with scientific proof that she is very EMF sensitive. Her health has worsened significantly twice with an unequivocal correlation to AMI smart meter installation. As a medical necessity her living environment must have the lowest possible EMF.

Accordingly, it is my unequivocal assertion that the installation of an AMI smart meter on Alexia McKnight's house is a strict medical contraindication. The only guarantee in this respect is to use an analogue meter.

Sincerely,

Peter J. Prociuk MD

Coughlin-Mck 1 Exh. 13
C-2017-2621057
4/10/18 Phila 3R

WS

From: **Smith, Ward L:(PECO)** ward.smith@exeloncorp.com
Subject: Your request for an ADA/Federal Rehabilitation Act Accommodation
Date: May 8, 2017 at 1:27 PM
To: alexia@mcknightinsight.com
Cc: Hannan, Tracy:(BSC) Tracy.Hannan@exeloncorp.com

Dear Dr. McKnight:

This responds to your email of March 16, 2017 to Tracy Hannan of Exelon's Legal Department. (The text of your email is reproduced at the end of this response.) In that email, you state that: "I am submitting this letter to you as a final request for a disability accommodation under the federal ADA and under Section 504 of the Rehabilitation Act of 1973."

PECO has reviewed the Americans with Disabilities Act and the Federal Rehabilitation Act with your request in mind, and concludes that those federal statutes do not provide a basis for an accommodation related to AMI meter installation. We are therefore unable to provide you with the requested ADA/Rehabilitation Act accommodation.

In your email, you further request: "Please accept this letter together with the medical letter from my physician (forthcoming in the US mail) and put a hold on any imminent AMI smart meter re-deployment while an accommodation is in process." As noted, we have completed the requested review and concluded that those statutes do not provide a basis for accommodation related to AMI meter installation. We are therefore unable to implement the requested ADA/Rehabilitation Act hold.

Ward Smith
Assistant General Counsel
PECO Energy Company

Text of initial email received on March 16, 2017:

Dear Attorney Hannan,
I am finally following up with you regarding a request for a disability accommodation. The attached letter sent to Mr. Craig Adams dated October 26, 2016 was not met with any success. The letter was very disappointingly funneled to the PECO AMI metering department which is not capable of handling disabilities. I am also attaching the written response from the metering department detailing their inability to understand and execute solutions to those with certain disabilities.
My letter to Mr. Craig Adams explains my medical problems that were markedly exacerbated following the deployment of the AMI wireless smart meter on my residence the first time on November 30, 2015. I reiterate again that these problems improved after the meter was removed, and began recurring again following meter re-deployment sometime in early-mid September 2016. I experienced symptom resolution again following removal of the meter on November 1, 2016. I am simply unable to tolerate the biological effects of that meter. It is unclear if this is due to the

am simply unable to tolerate the biological effects of that meter. It is unclear if this is due to the RF pulses it emits and/or the high frequency transients potentially placed on the transmission lines and household wiring.

This electrical hypersensitivity renders me unable to participate in normal daily activities. I can no longer tolerate going to church, restaurants, and other public and private places where cell phones, wifi, and other electromagnetic fields are so commonly prevalent. Most notably I experience immediate headaches that can linger for hours after even a short exposure. Longer exposures will cause notable memory impairment, cognitive dysfunction, sleep disturbances, and cardiac arrthymias among other ailments. To achieve relief, I simply avoid going places and remain secluded in my home where there is very low electromagnetic fields and currently still no meter on my house, courtesy of another unrelated electrical problem (stray voltage) which PECO is in the process of addressing.

I first complained of stray voltage on the house electrical grounding system March 21, 2016 through PECO's customer service. It has been nearly a year, and the problem remains, though construction has finally started on this project. Although resolution of the stray voltage is long overdue and welcomed, I expect that PECO plans to re-deploy the AMI smart meter again very soon.

I am submitting this letter to you as a final request for a disability accommodation under the federal ADA and under Section 504 of the Rehabilitation Act of 1973. I cannot accept an electrical meter on my home that very clearly exacerbates my health problems and makes my home uninhabitable for me. I propose continuing to estimate my electrical usage as we have been already doing for about 6 months out of the past year by keeping the same plate on the electrical box until PECO can locate a permanent electromechanical analog meter for accurate readings.

Please accept this letter together with the medical letter from my physician (forthcoming in the US mail) and put a hold on any imminent AMI smart meter re-deployment while an accommodation is in process.

Hard copies of this email and the attachments, including Dr. Prociuk's medical letter, will be sent via certified receipt in the US mail today.

Thank you for your attention.

Sincerely yours,

Alexia McKnight
PECO account number: 89900-01209

Co-plaint McKnight Exhibit 4
C-2017-2621057
4/10/18 Phila 3m

PECO
An Exelon Company

October 19, 2016

ALEXIA MCKNIGHT
258 HEYBURN RD
CHADDS FORD PA 19317

Dear Alexia,

Thank you for contacting PECO to express your concerns regarding PECO's upgrade of its automated metering system. Accordingly, I want to provide you with some additional information that I think you will find helpful about the technology that PECO is using for its system upgrades.

The upgraded meters we are installing are known as Advanced Metering Infrastructure (AMI), and are based on similar technology to that which PECO currently uses. All upgraded equipment, just like our existing AMR system, meets Federal Communications Commission (FCC) requirements.

Essentially, the difference between the AMR (existing) and AMI (upgraded) technologies is their ability to provide additional information to customers about how they use energy. This additional information is captured through the technology in the new meter and will be provided to customers through a Web-based application. The AMI meters that PECO is installing also contain a device that will allow the meters to communicate with compatible, customer-purchased devices in the future. Currently, these functions are not enabled, but they may be at a future date. Again, the AMI meters and these functions communicate in the same way as the meters currently in use, with lower cumulative radio frequency (RF) emissions. Cumulative RF volumes, including the typical distance and duration of transmissions of the AMI meter technology that we've selected for this project, are not just lower than that of many other household devices including a cell phone, but in fact are several orders of magnitude - more than 500 times - lower (0.19 milliwatts per square centimeter for a cellular phone versus 0.00037 milliwatts per square centimeter for an AMI meter). Also, unlike the cell phone which is most often held up to the ear, or a microwave oven which is most often located in a heavily-trafficked area of the home, most meters in PECO's service territory are located outside the home or in customer basements, resulting in decreased RF level with the additional distance.

With regard to privacy, your security is one of our top priorities. That is why this system will be a physically-secured, PECO-owned, private, encrypted, fiber optic and wireless system – ensuring the privacy and security of your energy usage information. We will also continue to work with the National Institute of Standards and Technology (NIST), the Federal Energy Regulatory Commission (FERC), and the Pennsylvania Public Utility Commission to ensure we continue to ensure the privacy of our system and your vital customer information. We also understand that customers may simply not want a new meter, but under Pennsylvania law (Act 129 of 2008) all Pennsylvania utilities are required to install new metering technology for every customer in our service territory.
Act 129 mandates strict timetables for system installation. While it may seem simple to allow some customers to "opt-out" of receiving an AMI meter, in fact, this would be extremely costly

as a second, manual data collection system would have to be established from the ground up for a small number of customers. And, shifting these costs onto the majority of customers would be unfair and inconsistent with sound public policy. Additionally, there are substantial operational advantages of automated metering that saves customers money, improves operational performance and reduces impacts to the environment through reduced truck rolls and emissions. Because of PECO's transition to AMR metering more than a decade ago, PECO customers have saved significantly, as expensive and less accurate manual collection of meter data was eliminated.

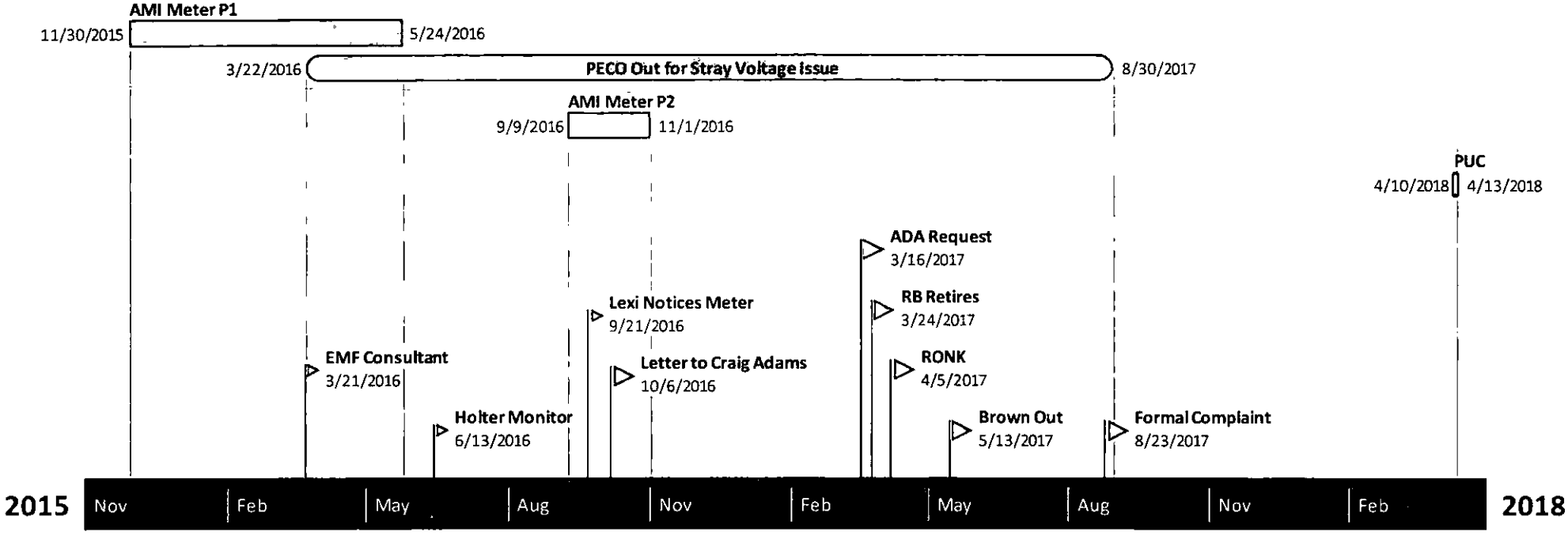
More importantly, our ability to respond to emergency outage events has been substantially enhanced due to automated metering technology. Three large storms in the last half of 2011 provided a great example of how advanced technology can help us respond to emergencies by enhancing our ability to know who's on and who's off -- the most critical information during any emergency event. During Hurricane Irene, for example, our ability to remotely test whether customers did or did not have service accelerated our ability to restore power to all of our customers by at least 24 hours. It would be a disservice to all our customers to eliminate these critical technological capabilities or create "blind spots" in our system that would slow restoration times for all. Operationally, partial deployment is impossible because our systems must provide coverage to all customers within a given geographic footprint. And, given the benefits our customers have experienced from our existing automated metering systems, we strongly believe these systems are in the broad public interest. We plan to replace the Sensus meter that is currently on your home with the L+G meter.

- PECO has worked closely with Underwriters Laboratory (UL), a leading testing and Certification Company, to establish a protocol for independent testing and analysis, which is now being replicated at utilities across the country.
- UL has conducted safety performance tests using the UL safety requirement for utility meters and found the meters we are using are fully compliant with these tests.
- PECO will continue to test and monitor its meters to ensure they meet the highest safety standards.
- As per the implementation order :
  Governor Edward Rendell signed Act 129 of 2008 ("the Act" or "Act 129") into law on October 15, 2008. The Act took effect 30 days thereafter on November 14, 2008. Among other things, the Act specifically directed that within nine months of its effective date, electric distribution companies ("EDCs") are to file, with the Commission for approval, a smart meter technology procurement and installation plan. 66 Pa.C.S. § 2807(f)(1). Each EDC smart meter plan must describe the smart meter technologies the EDC proposes to install, upon request from a customer at the customer's expense, in new construction and in accordance with a depreciation schedule not to exceed 15 year."
- Scientific studies have not identified any health concerns associated with the AMI meter.

Should you have any further questions, please feel free to contact me directly at (215) 841-4298.

Sincerely,
Brenda Eison
Customer Care Manager

Complaint McKay 4
Exh. C-15
C-2017-2621057
4/10/18 Phila. 32



PECO Events at 258 Heyburn Rd.

Nov. 30 2015. Smart meter gets installed, about 1:20pm.

Mar 21 2016 Called PECO to come and check their equipment. Sal pointed out to us over the weekend on Mar. 19 during his EMF evaluation that we carry an unacceptable voltage on the house ground. PECO was supposed to come today but didn't.

Mar 22 2016 Non-PECO man comes following my complaint that there is 1.5-6V on the house ground. He confirmed the voltage leak is at their end, not our house. He also said the only ground problem he's seen before was 120V or nothing, not a slow leak like we have—2-6V. Thus, the problem is beyond the tech's expertise or department, so he indicated it will escalate up now. I also told him that I measured a voltage on my neighbor's ground as well, which I did early this morning.

Mar 30 2016 I called PECO back to complain again this morning that my ground still carries several volts 10 days after my first call, and a guy in a PECO truck came a few hours later. He did the same thing as the first guy, playing with the meter, testing the connections, taking off the panel under it, taking off their neutral, etc.... Apparently there were no records of the first guy's visit and/or what he did. He said he confirmed 1 volt on something, and ordinarily they don't worry about that (it's within their 5% tariff range, something like that), but since I complained that it goes higher than that sometimes and my computer equipment shuts off sometimes he called somebody else who is expected to come and do a power quality test.

April 6 2016 About 3:30pm. Power suddenly goes out. I assume it's PECO working on the neutral failure problem. I call Tom Kology to see if they lost power, and he tells me there is a 'brush' fire across the street in front of the Cwyk house on the far side of Heyburn. I went to take pictures. A witness indicated there were sparks coming from the splice in the wires above.

April 7 2016 Russell calls and says he'll come the following morning. I told him about the fire on Heyburn Rd. yesterday and he said he'd investigate it.

April 8 2016 PECO comes back—Russell. When asked what started all this, I said there was occasional flickering lights, computer equipment shutting off, sensitive devices in the house acting funny (me). The dog approached a metal water pipe and suddenly jumping back. I mentioned the fire again.
He confirmed the fluctuating neutral of a few volts and drove off trying to check more of the lines on the street. He promised he'd get back to me later today with some findings. He may even want to put a recorder on the house he said.

May 2 2016 Monday May 2 or Tuesday May 3rd? Called PECO to swap out meter for one with less RF emissions. I measured and recorded the emissions and they are much more frequent than the interrogatory answers indicate they should be, They can't swap out the meter anytime soon, minimum of 5 days apparently. So scheduled to swap out on Saturday, May 7.

May 7 2016 Saturday. Waited all day for PECO to swap out meter. Nobody ever came. Nobody ever contacted me again about how they resolved this problem.

May 9 2016 Monday. I was gone all day. The house isn't quite as uncomfortable, not sure why. A bit less headaches and less heart palpitations. Wondered if PECO either reprogrammed the meter or came out and swapped it out, but the serial numbers are identical, so I wonder if they just reprogrammed it. ???

May 17 2016 Called and asked for Brenda Eisen. I left a message for her to return my call and schedule an appt. She never called me back!!!

May 17 2016 Call PECO emergency line. Got shocked in the bathtub.

May 18 2016 PECO comes (Mike from emergency response and Russell again from Power Quality). Mike confirms 4V on bathtub ground

May 24 2016 PECO-Chris and Russell from Power Quality back out again and seem to think something about Frank's house is interferring with my electricity, causing the neutral to fluctuate They say they do not need to put the smart meter back on the house. SMART METER GONE, alleluia!!

Monday May 30 2016—another strange electrical sting on my skin in the bathtub. That's the second time that's happened.

Jun 2 2016. Chris from PECO Power Quality here to tell me he and Russell plan to be here tomorrow around 9am to disconnect us from Frank's house, put us on our own transformer, put a recorder on our house, and see if the stray voltage problem goes away.
Jun 3. No PECO today.

June 6 2016—sting in bathtub again.

Wed Jun 7 2016— paint out on Heyburn Rd at telephone poles, like PECO-related somebody was here. I was gone all day. My iMac was powered off when I got home. The smart meter seemed moved (I think) from the ground to the top of the generator. Still off the house, thank you boys!!! I wonder if PECO was here.

August 2016 (before or on Aug 23rd)- Luis Figueroa and colleague (PECO engineering) knocks on door and indicates a fix to the problem will be a new transformer closer to the house. Frank's house will be on a separate feed from it, going to his house under the driveway. I ask if they can put my analog meter from the internet back on the house so we are no longer estimated.

Sep 14 2016- I emailed Luis for an update. No answer.
Sep 16 2016-I call Luis for an update. No answer. Left message

Sep 19 2016-call Luis back on his office phone. He answers! Still trying to get a hold of the realtor department to sign the contract and the papers, he says. Will keep bugging them later today again and tomorrow morning if necessary. He said he could put in an emergency bid

once they call and finalize the documents, so hopefully it can speed along a bit faster than the typical month. Gracious these people are slow!

September 21 2016— Notice that the smart meter had been placed on the house. Must have been a week or two ago. The bill suggests it was around September 9.

October 6 2016: Send registered letter to Craig Adams, CC: Christopher Crane and Umer Saleem, MD. Explained my problem and asked for an ADA accommodation. Written date Sep. 27.

October 18 2016: PECO representative called, confirming receipt of my certified letter. "Someone will be contacting me by phone within 24 hours"

October 18 2016: Larry called Customer support and talked to Chesway. He reported that our bill has a large credit, and wanted to explain that the plate had been on the house and we are being undercharged, thus the credit is not accurate. Chesway assured him that the estimates were accurate and there is no additional action required. We were overcharged, she says, and now we have a credit.

October 26 2016: I call PECO customer service, talked to Willy, and mentioned I had been waiting over a week for that return phone call I was supposed to get 24 hours after October 18. I was on hold most of the time but got a handful of apologies as I was supposed to hear back. But, today, by the end of the day... 'somebody from the executive office is supposed to get back to me'...
Irida Collaku 215-841-4540 direct number, calls back. AMI department. Brenda Eisen is her boss. I have 3 issues to be addressed:
1. Disability accommodation. 2. Fix stray voltage. 3. Return analog meter
Irida calls back 2 more times. 2nd conversation she tells me that, regarding my disability, it is federal law. They cannot replace the AMI meter. Suggests I talk to Brenda Eisen directly then, because she does not understand ADA or Section 504 and cannot help me. I said we may have the wrong department and I ask for this to be escalated to the highest authority that can handle disabilities.

October 28, 2016. I contact Russell Brocato and Luis, trying to find out what is taking so long, and to complain about the ill effects from the smart meter. I told Russell I really don't want to go through another Christmas holiday feeling so ill. He agreed to come out on Monday and put the plate back on for me!!!!!

November 1, 2016: Russell and Chris come back to re-assess the stray voltage problem and apologize it's taken so long—internal PECO bureaucracy unfortunately. Russell removes the SM for us again. Russell is my new super hero!!!

March 7, 2017 — Miller Bros. start construction on driveway, laying conduit from telephone pole to the split to Frank's house. Finished on March 9.

March 16, 2017. Sent ADA disability accommodation request to Tracey Hannan via email and certified receipt US mail.

March 23, 2017 — Miller Bros. comes to put in Frank's line through the conduit.

March 24, 2017— Russell retired.

March 27, 2017 — Miller Bros. comes and finally disconnect's Franks house from ours. Ground voltage started at ~1V before they started and didn't change noticeably at all. But was low voltage and no load— neither Frank nor Janet were home. I expect the low voltage to stay low during cold and loads now. The 45kHz peak remains, as most of the other high frequencies on the ground.

April 5, 2017 — PECO power quality (Dennis, Chris, and foreman Bob Jones), all out here to install ronk. ~1.5V on house ground went to ~0.6V after ronk. Dennis said this would be zero with 1000ohm in the line. PECO was very puzzled though about why there was still voltage on the neutral at the house end (not connected to the house), but they weren't getting it at the street end. They thought of calling Miller Bros. and finding out what they might have done to get some explanation. I think they were also going to better investigate the neutral to the substation—Chris said something like that...

April 26, 2017 — Miller Bros. back out to finally patch up the driveway. Job completed!

May 13, 2017 — No water this morning. Thought is was a broken water pump, but turns out the A Bus was losing voltage—down to 60V. The basement lights started dimming, then they went out completely. The hot water seemed to go out, too. Larry started up the generator and the water came back, the lights came back, both polarities returned to 120Vs again. The well pump guys came out and got strange voltage and current on their lines to the pump, but the pump tested fine. Called PECO (ER hotline a real pain to get through). PECO man Elliot comes out shortly after call and confirms one 'bad leg' coming into the house and 9V on the neutral.

May 14, 2017. Mother's Day — Chris and another Chris from Power Quality come back out and confirm the problem. Must have a short in the line between the transformer and the house. Suspected to be under the driveway with the recent Miller's Bros. excavation. Two other guys come out and put a yellow box —some type of special transformer to convert the one good polarity into two 120V polarity to get us off the generator. The problem is temporarily fixed until other guys come back and dig up the driveway/yard to find the short.

August 23, 2017. Formal complaint transmitted 8/23, filed on 8/24 8am, complaint: Violation of Section 1501. This is submitted so PECO cannot try to put a smart meter on this house anymore.

August 30, 2017: I'm in Texas. Larry reports in a text "PECO out today and removed the phase saver box, hooked up normal line. We have 120 on both A/B side. Stray

voltage 0 at the box, 0.34 on your yellow (volt)meter. And...😉, no smart meter installed. We still have the plate".

Sep. 13. Shawane Lee responds to my formal complaint.

Jan. 25 phone rings. PECO Energy. Robot telling me that a technician that I had previously scheduled would be out tomorrow. He should contact me before showing up. I certainly did not schedule an appointment to have a tech out.

Jan. 26. guy from Grid One in my driveway. Said he was sent by Peco to install a smart meter on the house. I emailed Judge Heep and Mr. Ward Smith to relay this information. Mr. Smith responds immediately indicating he will check up on this immediately. About an 1 hr. 20 mins later he relays an explanation that is mostly fiction with a few scattered facts.

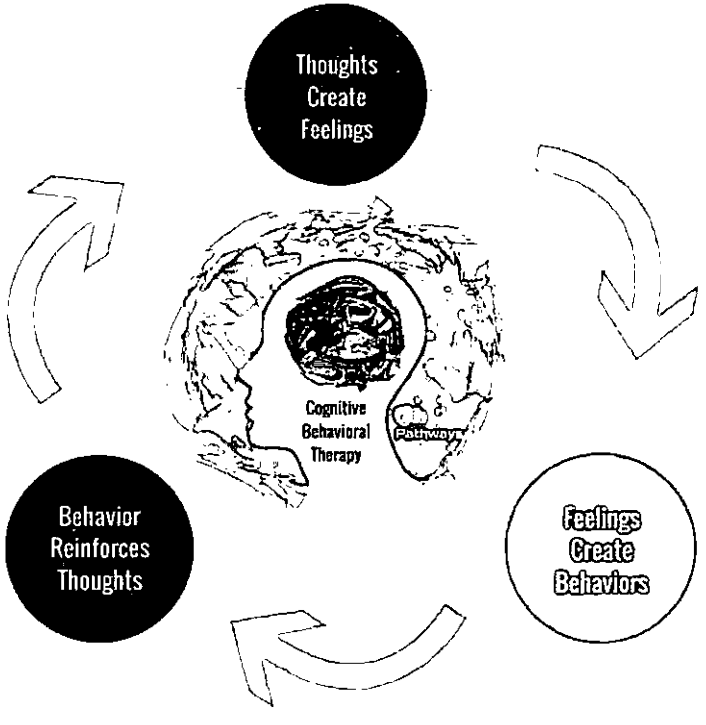
Mar. 14. PECO bucket truck at the end of the driveway. They are putting a green bag under my transformer. It's the afternoon, the same day that I email the judge to explain I need more witnesses and the need for more court days. The reason for this is unknown. I did not request any service or report any complaints. There were no outages. We were not notified directly.

Mar. 20. Late morning, before noon, PECO bucket truck back out to take green bag down off transformer. I think it might have been Dennis. I talked to him, asked what he was doing. He said he was sent over to check voltage.

Complaint McKnight Exhibit 6
C-2017-2621057
4/10/18 Phila SR

Cognitive Behavior Therapy

CBT and Nocebo

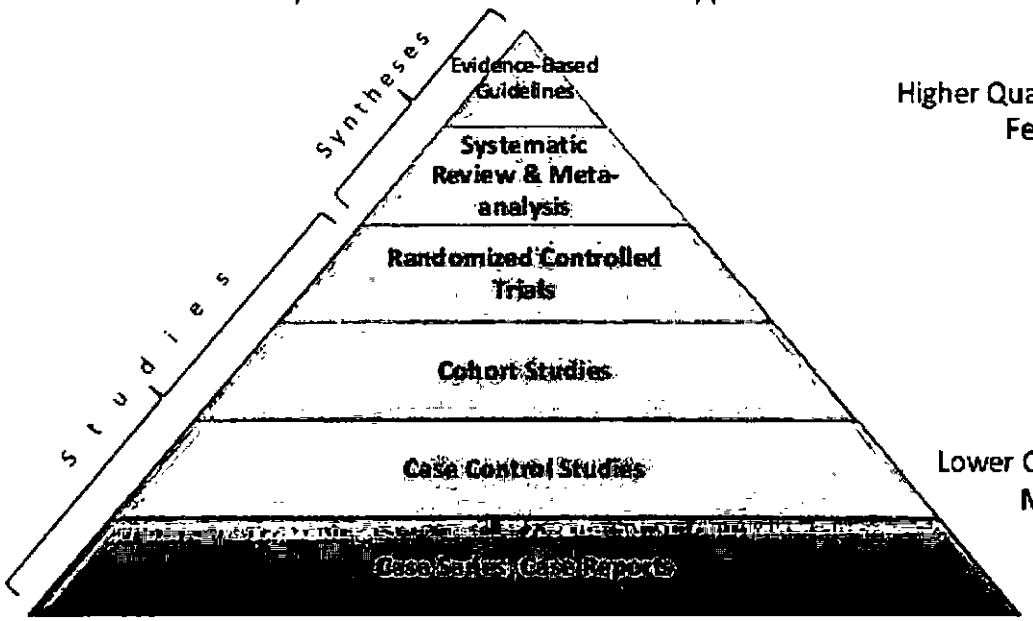


Nocebo is a phenomenon in which inert substances or mere suggestions of substances actually bring about *negative* effects in a patient or research participant
Nocebo and **means** "I shall harm"
whereas placebo **means** "I shall please.

Amplification is used to describe a judged tendency of a person to **amplify** physical **symptoms** based on psychological factors such as anxiety or depression.

Classical Conditioning a learning process that occurs when two stimuli are repeatedly paired; a response that is at first elicited by the second stimulus is eventually elicited by the first stimulus alone

Evidence Pyramid – Publication Types

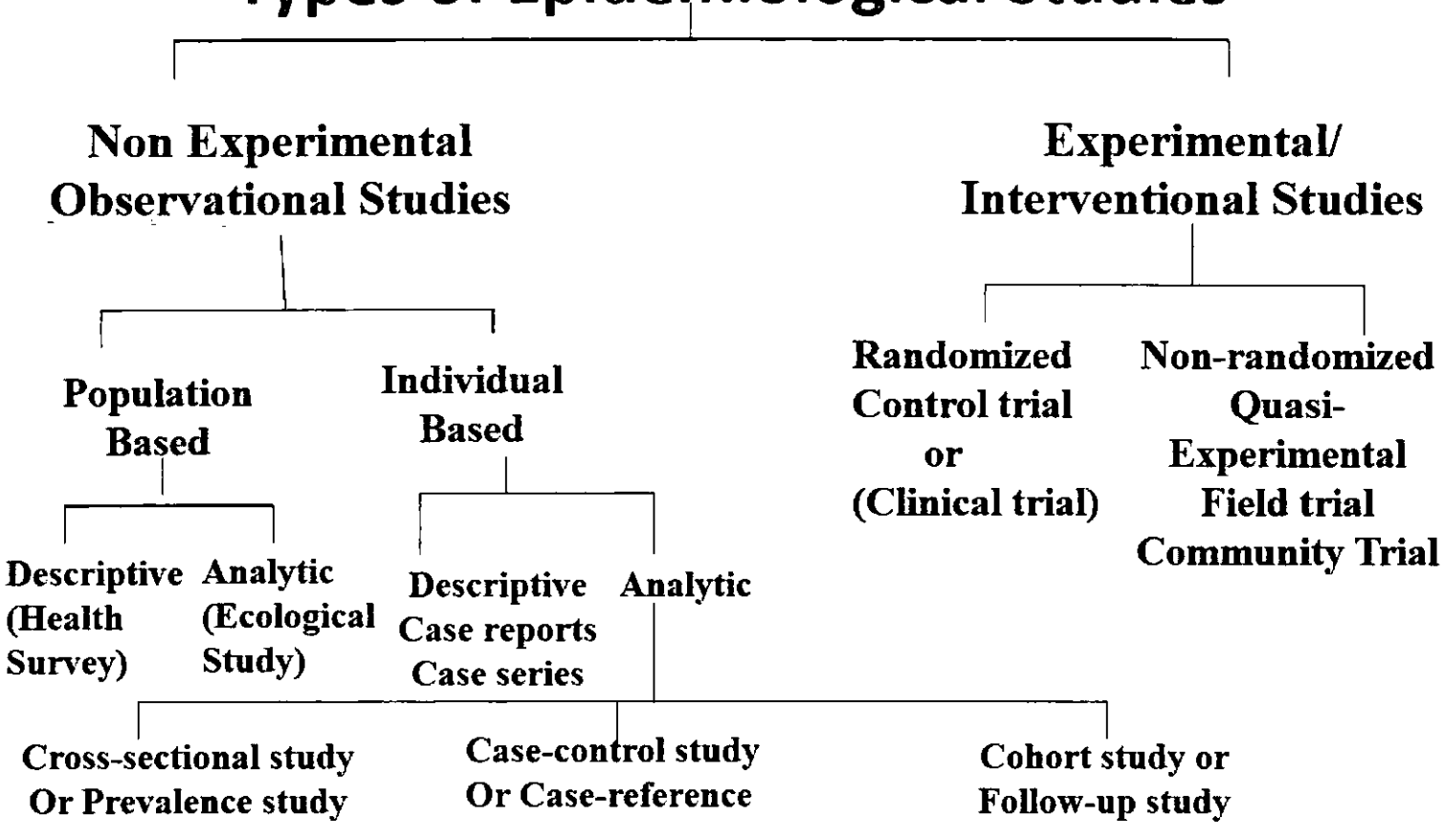


Generalization

Higher Quality of Information
Fewer Articles

Lower Quality of Information
More Articles

Types of Epidemiological Studies



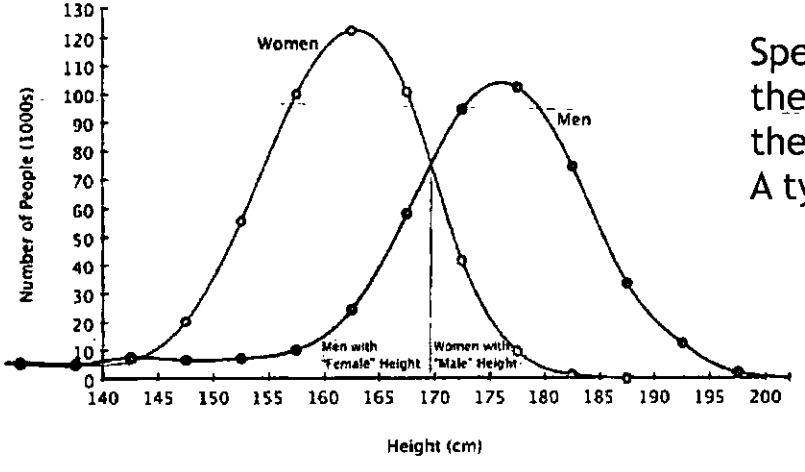
Domain Study Types

Type of Question/Domain	Type of Study/Methodology
Therapy/Treatment Selection of treatment or interventions that do more good than harm and that are worth the effort and cost	Double-Blind Randomized Controlled Trial Systematic Review/Meta Analysis of RCT
Diagnosis Selection and interpretation of diagnostic tests, in order to confirm or exclude a diagnosis, based on considering their precision, accuracy, acceptability, expense, safety, etc.	Controlled Trial Systematic Review/Meta Analysis of Controlled Trial
Prognosis Estimation of a patient's likely clinical course over time and anticipation of likely complications of disease	Cohort Studies, Case Control, Case Series
Harm/Etiology Identification of causes or risk factors for disease	Cohort Studies
Prevention	Randomized Controlled Trial, Cohort Studies
Quality Improvement	Randomized Controlled Trials

Why not RCT?

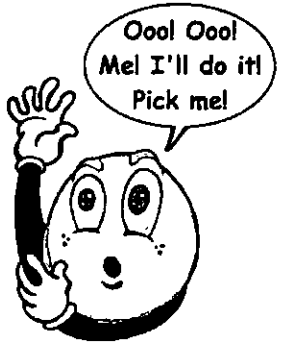
1) Unethical to Randomize
2) Effects may be Rare
3) Effects may be Delayed
4) Follow up / Drop outs
5) Expense limits size

Bias is a systematic error in the design or analysis that results in a mistaken estimate



Spectrum bias (a.k.a. case mix bias) exists when the population under investigation does not reflect the general population or the clinically relevant population. A type of Selection Bias

"Would you like to sign up for a headache, so that I can show you that your problem is that you have a thought disorder?"



Uncertainty

X does not cause Y
Certain

I don't know if X causes Y
Uncertain

X causes Y
Certain

P	Q	PANDQ
TRUE	TRUE	TRUE
TRUE	FALSE	FALSE
FALSE	TRUE	FALSE
FALSE	FALSE	FALSE

P	Q	PORQ
TRUE	TRUE	TRUE
TRUE	FALSE	TRUE
FALSE	TRUE	TRUE
FALSE	FALSE	FALSE

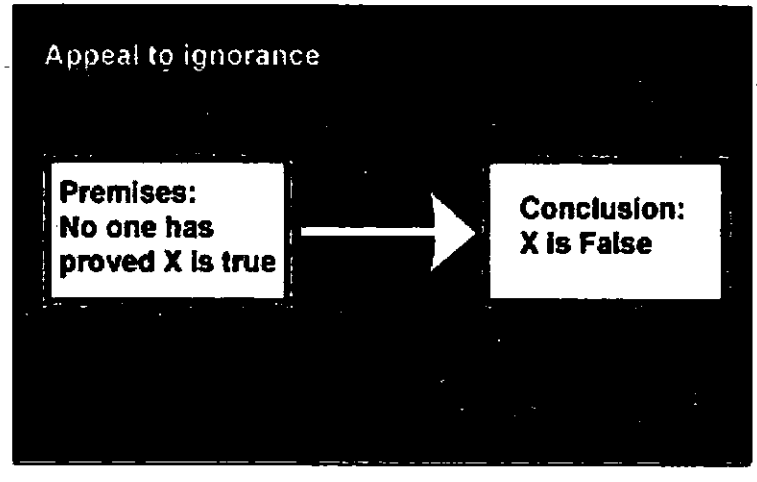
P	Q	PANDQ
TRUE	UNCERTAIN	UNCERTAIN
UNCERTAIN	TRUE	UNCERTAIN
FALSE	UNCERTAIN	FALSE
UNCERTAIN	FALSE	FALSE
UNCERTAIN	UNCERTAIN	UNCERTAIN

P	Q	PORQ
TRUE	UNCERTAIN	TRUE
UNCERTAIN	TRUE	TRUE
FALSE	UNCERTAIN	UNCERTAIN
UNCERTAIN	FALSE	UNCERTAIN
UNCERTAIN	UNCERTAIN	UNCERTAIN

Appeal to Ignorance

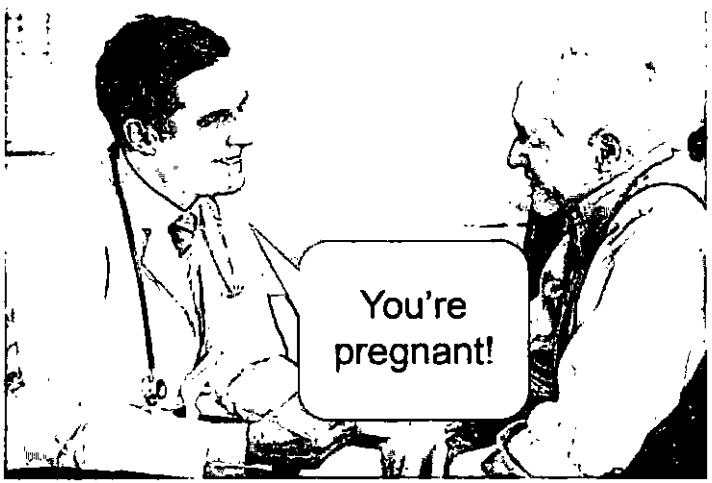
premise 1
premise 2
premise *n*
} Nothing is known about "X"

Conclusion } We know something about "X"



Types of Errors

Type I Error



False Positive

Type I Error if we say 'medical basis exists' but in reality there is no basis

Type II Error

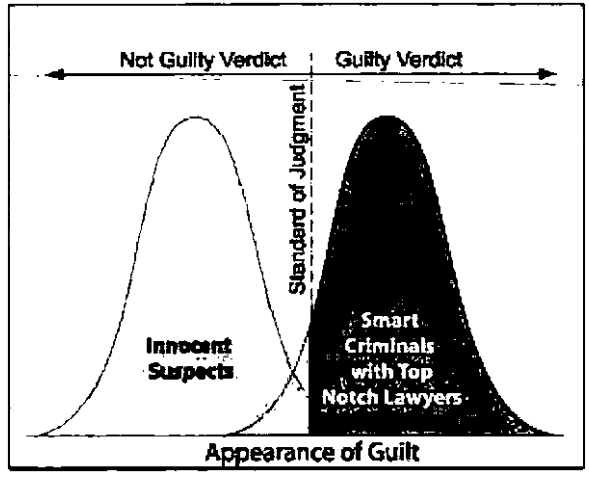
False Negative

Type II Error if PECO says 'no medical basis' but in reality there is a 'medical basis'

Decision under Uncertainty:

McKnights Win but
Lexi didn't have EHS
(We made type I error)

PECO has inconvenience
to read an analog meter



PECO Wins but
Lexi Has EHS
(PECO made type II error)

Lexi Gets Harmed

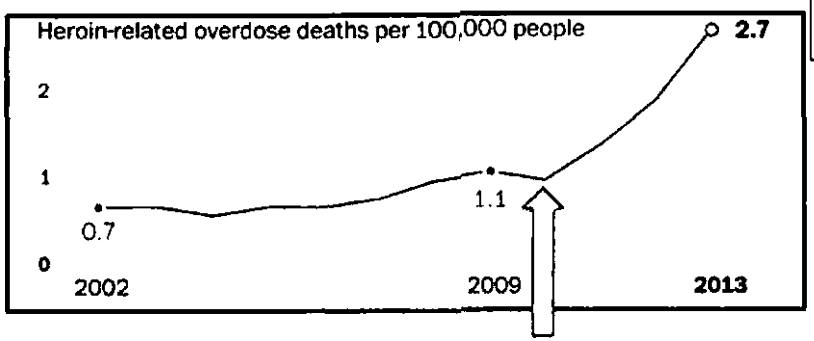
Letting a guilty criminal free

"beyond reasonable doubt"

Convicting an innocent person

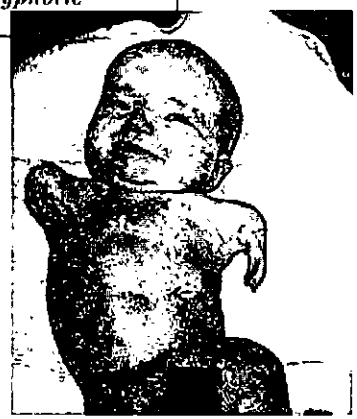
Would you get on a plane if the pilot said there was a 97% chance that it will make it, but a 3% chance that it will crash?

Appeal to Authority



Abuse-resistant OxyContin Approved

Source: National Survey on Drug Use and Health: National Vital Statistics System, CDC



Arguments from authority carry little weight – authorities have made mistakes in the past. They will do so again in the future. Perhaps a better way to say it is that in science there are no authorities; at most, there are experts

CARL SAGAN
WORDPORN.COM

Electromagnetic Hypersensitivity: A Systematic Review of Provocation Studies

G. James Rubin, PhD, Jayati Das Munshi, MBBS, and Simon Wessely, MD

Objectives: The objectives of this study were to assess whether people who report hypersensitivity to weak electromagnetic fields (EMFs) are better at detecting EMF under blind or double-blind conditions than nonhypersensitive individuals, and to test whether they respond to the presence of EMF with increased symptom reporting. **Methods:** An extensive systematic search was used to identify relevant blind or double-blind provocation studies. This involved searching numerous literature databases and conference proceedings, and examining the citations of reviews and included studies. The results of relevant studies were tabulated and metaanalyses were used to compare the proportions of "hypersensitive" and control participants able to discriminate active from sham EMF exposures. **Results:** Thirty-one experiments testing 725 "electromagnetically hypersensitive" participants were identified. Twenty-four of these found no evidence to support the existence of a biophysical hypersensitivity, whereas 7 reported some supporting evidence. For 2 of these 7, the same research groups subsequently tried and failed to replicate their findings. In 3 more, the positive results appear to be statistical artefacts. The final 2 studies gave mutually incompatible results. Our metaanalyses found no evidence of an improved ability to detect EMF in "hypersensitive" participants. **Conclusions:** The symptoms described by "electromagnetic hypersensitivity" sufferers can be severe and are sometimes disabling. However, it has proved difficult to show under blind conditions that exposure to EMF can trigger these symptoms. This suggests that "electromagnetic hypersensitivity" is unrelated to the presence of EMF, although more research into this phenomenon is required. **Key words:** electromagnetic hypersensitivity, provocation studies, systematic review.

EHS = electromagnetic hypersensitivity; **EMF** = electromagnetic field; **SMD** = standardized mean difference; **UMTS** = universal mobile telecommunications system (a "third-generation" mobile phone signal); **VDU** = visual display unit.

INTRODUCTION

"Electromagnetic hypersensitivity" (EHS) is a relatively new phenomenon in which sufferers report a range of symptoms that are apparently triggered by the presence of weak electromagnetic fields (EMFs) (1). These symptoms show no cohesive pattern (2,3) but are typified by nonspecific sensations such as sleep disturbance, headaches, fatigue, and subjective cognitive problems (2,3). In its more severe form, EHS can be disabling, preventing sufferers from pursuing normal work or social lives.

The electromagnetic triggers for the symptoms reported by EHS sufferers are diverse. Although a list of the more common would include visual display units (VDUs), mobile phones, mobile phone base stations, fluorescent lighting, overhead power lines, and household items such as televisions and microwave ovens (3), not all sufferers report being sensitive to all potential triggers and many report only 1 or 2 specific electrical items as being problematic. The EMFs emitted by these devices vary considerably and encompass frequencies in the radio, microwave, kilohertz, and extremely low-frequency ranges (3). In almost all cases, however, the intensity of the EMFs that seem to trigger EHS symptoms is far below that known to cause physiological changes in animal models (4,5).

The underlying causes of EHS are the subject of considerable debate. On the one hand, it has been proposed that biophysical factors may make a minority of people particularly sensitive to EMF, with mechanisms involving the release of histamine by mast cells (6) having been suggested. On the other hand, it has also been proposed that the condition may be more psychologic than physicochemical (7), with symptom amplification and classic conditioning being important. Clearly, the appropriate treatment and management of EHS will depend on which of these models is correct. The best way to determine this is to examine the results of blind and double-blind experimental provocation studies. These experiments typically expose volunteers with self-reported EHS to 2 conditions, an active condition in which weak EMFs are presented and an inactive condition in which they are not. Two outcomes can then be examined: the participant's ability to correctly discriminate active from inactive (their "electromagnetic sensibility") and the participant's tendency to experience more symptoms in the active condition (their "electromagnetic hypersensitivity") (8). Although electromagnetic sensibility may be a necessary precondition for EHS, it is certainly not sufficient as there is evidence that healthy individuals can display heightened sensibility without necessarily experiencing symptoms as a result (8).

Two previous reviews have looked at provocation studies for EHS in some detail. In 1997, a report for the European Commission (1) described the results of 13 such experiments and concluded that, although "'electromagnetic hypersensitive' people do react in these provocation studies, [. . .]these reactions have not been shown to be related to the fields." More recently, a systematic review considered the results of 8 experimental studies published in peer-reviewed journals before coming to a similar conclusion (9).

The systematic review reported here attempted to identify all blind or double-blind provocation studies for EHS that could help to answer the following questions: are people who are apparently hypersensitive to weak EMFs better at detecting these fields under blind or double-blind conditions than nonhypersensitive individuals, and do they respond to the presence of weak EMFs with increased symptom reporting?

METHODS

Search Strategy for the Identification of Studies

The following electronic databases were searched for potentially relevant studies: AMED, ASSIA, Cinahl, the Cochrane Collaboration Library, Em-

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0033-3174/05/6702-0224

base, Index to Theses, the Institute of Electrical and Electronics Engineers EMF research database, ISI Proceedings, ISI Web of Science, Medline, Psychinfo, and the World Health Organisation EMF research database. These were searched from inception to January 2004 for a wide range of MeSH or free-text key words relating to EHS, including, for example, "electrical sensitivity," "electromagnetic hypersensitivity," "electro-smog," "techno-stress," "screen dermatitis," and "environmental illness." The databases were also searched for papers using combinations of relevant stimulus MeSH or free-text key words (eg, "mobile phone," "computer," "power line") and hypersensitivity MeSH or free-text key words (eg, "allergy," "hypersensitivity," "intolerance").

In addition, the Bioelectromagnetics Society conference proceedings for 1996 to 2003 were handsearched, as were the documents available on the COST 281 web site. The reference sections of any pertinent studies and reviews were also examined for additional references.

Inclusion Criteria

Only blind or double-blind experimental provocation studies were eligible for inclusion in the review, with a provocation study defined as any experiment in which the participants were systematically exposed to higher EMFs in 1 experimental condition than in another. Because we were interested primarily in the effects of ambient EMF, studies in which an electrical current was directly applied to participants were excluded (e.g. 10).

Eligible studies were required to test a discrete sample of participants who reported symptoms associated with low-intensity manmade electromagnetic stimuli. This attribution had to have been explicitly made by either the participants themselves or the experimenters. So, for example, studies investigating symptomatic VDU users in which no attribution of the symptoms to the VDU had been explicitly made (e.g. 11) were excluded, as were studies in which participants reported symptoms that were suspected to be the result of visual or ergonomic features of the VDU. Studies that examined the putative effects of EMFs on healthy volunteers alone were also excluded.

Finally, only studies reporting data relating to certain outcomes were included in the review. In particular, we were only interested in experiments that examined outcomes that are central to the self-diagnosis of EHS, ie, subjective symptoms, physical signs such as observer-rated skin rash and subjective perception of whether EMF is present. Proxy measures of ill health such as blood tests or skin biopsies are less relevant to this process of self-diagnosis and are not covered in this article.

Data Extraction and Analysis

Details regarding the following aspects of each included study were extracted and tabulated: sample (n, details regarding any control sample), stimuli (type of provocation), design (number and length of provocations per participant), sensibility results (total number of provocations correctly identified as active or inactive by participants, number of participants classified as able to discriminate active from inactive), and hypersensitivity results (type of self-reported symptoms or other relevant health outcomes measured, significance level of any difference).

Metaanalyses were conducted to determine whether the proportion of EHS participants apparently able to discriminate active from inactive conditions was greater than the corresponding proportion of control participants.

Review Process

The literature searches, assessments of inclusion, and data extraction were conducted by Gideon James Rubin with uncertainties resolved through consultation with the 2 coauthors. Where uncertainty existed as to whether 2 papers reported data from the same experiment, clarification was sought from the authors of the original papers.

RESULTS

Search Results

In total, approximately 8600 titles or abstracts were examined from which 497 papers were selected as potentially relevant to the review and examined in full. Of these, 372 were excluded because they were review papers, editorials, duplicate publications, or did not include a sample of people whose symptoms were explicitly attributed to EMF. A further 83 did not describe provocation studies, and 13 reported unblinded provocations.

Details relating to 31 individual provocation experiments involving 725 EHS participants were included. Thirteen experiments (213 EHS participants) used VDU-related provocations as their active exposure condition, 7 (161 EHS participants) examined mobile phone-related provocations, 10 (315 EHS participants) examined other EMF provocations for participants with generalized EHS, and 1 (36 EHS participants) tested an apparently healthy group of volunteers categorized as electromagnetically hypersensitive based on a median split for the results of a single questionnaire item.

Visual Display Unit-Related Experiments

Details regarding the 13 VDU-related experiments are given in Table 1. Of these, 1 reported significantly worse symptoms in the active condition than in the sham condition for 1 of the 10 tests conducted (standardized mean difference [SMD] = 1.0, $p < .01$) (12), although the authors suggested that this result probably reflected a type 1 error caused by multiple significance tests. A second study found that more EHS participants reported a reduction in skin "tingling, prickling or itching" after 2 weeks of work with an activated electric-conductive filter fitted to their computer screen compared with 2 weeks of work with a deactivated "placebo" filter fitted (13). However, this effect was small (mean difference = 0.1 on a 10-point scale), no other symptoms were affected, and the authors were subsequently unable to replicate this finding in a larger study with a longer exposure period (14). Of the remaining 10 studies, none found any evidence that EHS participants had greater sensibility than healthy controls or experienced more symptoms in active compared with inactive conditions (7,15–22).

Two of the 99 EHS participants (2.0%) for whom information was available in these studies appeared to be reliably able to discriminate EMF from sham conditions, compared with 1 of 32 healthy controls (3.1%). This difference was not statistically significant (chi-square = 0.13, $df = 1$, $p = .72$).

Mobile Phone-Related Experiments

Details of the 7 studies relating to mobile phone hypersensitivity are given in Table 2. One of these reported that a single participant of the 7 tested could detect whether a mobile phone hidden inside a bag was "on" or "off" 9 times out of 9 (23). Unfortunately, this study did not include a nonsensitive control group. Moreover, in an as-yet unpublished study, the same group previously used similar methods to test "about 70" EHS participants 3 to 12 times each without finding any who could reliably make this discrimination (Johansson, personal communication), suggesting that the significant finding may be a statistical artefact caused by repeated testing.

In another study, Zwamborn et al. (24) reported that exposure to a universal mobile telecommunications system

TABLE 1. Provocation Studies for Visual Display Unit-Related Sensitivities

Reference	Sample	Active Stimulus	Number and Length of Exposures	Results (all $p > .05$ unless otherwise indicated)		
				Total Number of Correct Discriminations Between Active and Sham (number of participants apparently demonstrating electromagnetic sensibility)	Comparison Between Electromagnetic Field Conditions for Self-Reported Symptoms	Comparison Between Electromagnetic Field Conditions for Other Health Outcomes
Nilsen, 1982 (17)	5 EHS	Exposure to a VDU	Two 6-hr provocations, 1 active and 1 inactive	Not measured	None	Observer-rated skin rash
Swanbeck, 1989 (18)	30 EHS	Exposure to moderate EMF VDU and low EMF VDU	One 3-hr provocation to each VDU	Not measured	Heat or reddening, itching, stinging, oedema, "others"	None
Hamnerius, 1993 (19)	30 EHS	Exposure to VDU-like magnetic fields	Up to 8 1-hr provocations, in pairs of active and inactive	EHS: 38/80 (0/30)	Unspecified symptoms	Erythema, observer-rated skin redness
Hellbom, 1993 (22)	6 EHS	Exposure to a VDU	Four 30-min provocations; 2 active, 2 inactive	EHS: 8/24 (0/6)	Symptoms—unspecified in translation	None
Sandstom, 1993 (20)	22 EHS	Various VDU provocations	Varying durations of exposure	Not measured	Skin tightness, heat, itching, pricking, aching, other	None
Oftedal, 1995 (13)	19 EHS	Normal office work with an active or inactive VDU filter	Participants worked for 2 weeks with each filter	Not measured	Heat, itching ($p = .03$), skin tightness, tenderness, redness, blisters/acne, desquamation	Observer-rated dermatologic status
Sjoberg, 1995 (12)	7 EHS, 5 healthy controls for a subset of provocations	Exposure to 3 different VDU strengths	Four active and 4 inactive 1-hr provocations for each exposure	EHS: 99/176 (0/7); control: not reported (0/5)	"Comparison with symptoms from (liquid crystal display) work" ($p < .01$); 9 other unspecified symptoms	None
Andersson, 1996 (21)	16 EHS	Exposure to a computer and VDU	At least 2 pairs of 30-min provocations (1 active and 1 inactive) before and after a period of cognitive behavioral therapy	EHS: 41/80 (1/16)	Unspecified symptoms previously reported by the participants as elicited by EMF	None
Keisu, 1996 (15)	1 EHS, 1 healthy control	Exposure to a personal computer	Ten provocations, each randomized to active or inactive	EHS: 6/10 (0/1); control: 5/10 (0/1)	Not measured	None
Oftedal, 1999 (14)	38 EHS	Normal office work with an active or inactive VDU filter	Participants worked for 3 months with each filter	Not measured	Heat, itching, skin tightness, skin redness, eye stinging, eye pain, eye redness, eye tiredness, sensitivity to light, headaches, dizziness, tingling, fatigue	None
Flodin, 2000 (16)	15 EHS, 26 healthy controls	Different provocations, most using a VDU	Two active and 2 sham exposures of up to 1 hr each	EHS: 29/60 (1/15); control: 30/60 (1/26)	Ten unspecified symptoms relating to skin, mouth, airways, abdominal sensations, mental sensations	None
Lonne-Rahm, 2000a (7)	12 EHS, 12 healthy controls	Exposure to a computer and VDU, with or without the presence of a stressor	One 30-min provocation to each of 4 conditions (VDU on or off, stressors present or absent)	EHS: 22/48 (0/12); control: not reported	Facial skin sensations, stress level, tiredness; no interactions were found between stressor and EMF condition	None
Lonne-Rahm, 2000b (7)	12 EHS, 12 healthy controls	Exposure to a computer and VDU, with or without the presence of a stressor	One 30-min provocation to each of 4 conditions (VDU on or off, stressors present or absent)	EHS: 29/52 (0/12); control: not reported	Facial skin sensations, stress level, tiredness; no interactions were found between stressor and EMF condition	None

EHS = electromagnetic hypersensitivity; EMF = electromagnetic field; VDU = visual display unit.

TABLE 2. Provocation Studies for Mobile Phone-Related Sensitivities

Reference	Sample	Active Stimulus	Number and Length of Exposures	Results (all $p > .05$ unless otherwise indicated)		
				Total Number of Correct Discriminations Between Active and Sham (number of participants apparently demonstrating electromagnetic sensibility)	Type of Self-Reported Symptoms Measured and Comparison Between Active and Inactive Conditions	Other Health Outcomes Measured and Comparison Between Active and Inactive Conditions
Johansson, 1995 (23)	7 EHS	Mobile phone hidden inside a bag	Participants exposed up to 9 times each; each exposure randomized as active or inactive; exposures lasted for twice the time necessary to provoke symptoms during a nonblind provocation	EHS: 25/37 (1/7 [$p = .002$])	None	None
Radon, 1998 (25)	11 EHS	GSM 900 signal	A series of 12 trials, each consisting of 3 2-min exposures, 1 active and 2 inactive	EHS: 54/132 (0/11)	None	None
Raczek, 2000 (27)	16 EHS	GSM 900 signal	A series of 21 trials, each consisting of 3 3-min exposures, 1 active and 2 inactive	EHS: 94/336 (0/16)	None	None
Barth, 2000 (26)	1 EHS	Mobile phone	Patient exposed to 15 active provocations and 16 inactive provocations	EHS: 13/31 (0/1)	None	None
Hietanen, 2002 (28)	20 EHS	Analog, GSM 900 and GSM 1800 signals	One 30-min exposure to each condition	EHS: not reported (0/20)	Number of symptoms reported by participants during experiment was greater in inactive condition (no statistical analysis)	None
Johansson, 2003 (unpublished data)	70 EHS	Mobile phones	Between 3 and 12 provocations per participant; exposures lasted for twice the time necessary to provoke symptoms during a nonblind provocation	EHS: not reported (0/70)	Unspecified symptoms	None
Zwamborn, 2003 (24)	36 EHS, 36 healthy controls	GSM 900, GSM 1800, and UMTS mobile phone base station signals	Each volunteer exposed to 3 45-min provocations, 1 inactive and 2 active	Not measured	Anxiety ($p < .05$) [B], somatic symptoms ($p < .05$) [B], inadequacy ($p < .05$) [B, E], depression, hostility ($p < .05$) [B, C]	Reaction time ($p < .05$) [A, E], memory comparison ($p < .05$) [D,E], selective attention ($p < .05$) [B, E], dual-tasking reaction time ($p < .05$) [D], filtering irrelevant information ($p < .05$) [A]

A, Comparison of inactive and 900 MHz for EHS group; B, comparison of inactive and 2100 MHz for EHS group; C, comparison of inactive and 900 MHz for control group; D, comparison of inactive and 1800 MHz for control group; E, comparison of inactive and 2100 MHz for control group.
EHS = electromagnetic hypersensitivity; UMTS = universal mobile telecommunications system.

(UMTS) mobile phone base station signal resulted in greater levels of anxiety, somatic symptoms, inadequacy, and hostility for EHS participants than exposure to a sham signal ($p < .05$). A healthy control group was also significantly more affected by the UMTS signal than the sham signal, experiencing an increase in inadequacy only ($p < .05$). These effects were smaller in the control group (overall SMD for well-being = 0.22) than in the EHS group (SMD = 0.36), although the authors of the study caution against direct comparison between the groups because of the demographic differences observed between them. Some changes in objective cognitive measures were also apparent for both samples as a result of exposure to UMTS, 900-MHz and 1800-MHz signals, although no consistent pattern was found in terms of which cognitive variables were affected by which type of signal (see Table 2). Furthermore, although some cognitive parameters (ability to filter information, reaction time) showed significant decrements as a result of exposure, others (memory, visual attention, dual-tasking reaction time) showed significant improvements.

Of the 4 remaining blind or double-blind mobile phone-related studies (25–28), none found any effect indicative of biophysical hypersensitivity.

Only 1 EHS participant (0.8%) of the 125 for whom information was available in these studies was consistently able to discriminate active from inactive exposures. No comparable data were available for any control participants. Nevertheless, the probability of 1 or more of 125 participants identifying "on" from "off" 9 times out of 9, as this participant did, but purely by chance, is $p = .22$.

General Electromagnetic Hypersensitivity-Related Studies

Ten studies tested individuals reporting EHS using provocations with other sources of weak EMF (Table 3). One of the earliest, by Rea et al. (29), tested 100 patients with EHS and comorbid "biological inhalant, food and chemical sensitivities." Of these, 16 individuals were identified who repeatedly responded to certain EMF frequencies with symptoms but who did not respond to inactive challenges. A control group of healthy volunteers showed no response to either type of challenge. Although the substantive parts of this study were described as double-blind, the authors reported that the exposure equipment and its operator were present in the testing room during the experiment. A subsequent attempt by this group to replicate their findings, but this time using a screen to prevent participants from seeing the manipulation of the exposure equipment, did not find any evidence of biophysical hypersensitivity (30).

Aside from this study, only 1 other in this category found any significant effect of EMF (31). This crossover experiment exposed EHS participants to 4 hours of nighttime EMF or an inactive sham condition over the course of 4 weeks. Measurements of mood during the morning revealed significantly higher levels of pleasure ($p = .01$) and arousal ($p = .05$) during the EMF condition, a finding that runs contrary to the self-reports of EHS sufferers. The explanation for these findings is still unclear, but given their unexpected direction, they do not seem to support the hypothesis that EHS sufferers are adversely affected by EMF. Of the remaining 7 studies, none identified any significant effect of EMF on EHS sufferers (32–38).

Six of 95 EHS participants (6.3%) and 1 of 47 control participants (2.1%) were reliably able to discriminate active from inactive conditions in these experiments, a nonsignificant difference in proportions (chi-square = 1.18, $df = 1$, $p = .28$).

Other Studies

One other study (39) was identified. This used a between-participants design to test a group of 66 volunteers drawn from student and military populations. Two of the 3 provocations used are particularly relevant here: exposure to EMF and noise, and exposure to noise only. Adjusting for performance in a third condition in which noise and EMF were not present, participants classified as hypersensitive were significantly more affected by the presence of EMF than control participants in terms of their performance on visual processing and visual attention tasks ($p < .05$). No such effects were seen for 3 other cognitive variables or for subjective discomfort (see Table 4). However, interpretation of these results is complicated by several methodologic factors, including the categorization of participants into sensitive or control groups on the basis of responses given after testing had been completed and the inappropriate use of 1-tailed significance tests.

DISCUSSION

Current Evidence

To date, 7 blind or double-blind provocation studies have found some effect of EMF provocation on people who report EHS (12,13,23,24,29,31,39). However, even the original authors have been unable to replicate the results of 2 of these (14,30), the results of 3 more seem to be statistical artefacts reflecting the large number of significance tests conducted (12), the large number of participants tested (23); unpublished Johansson study), or the inappropriate use of 1-tailed significance tests (39), and the results of the remaining 2 are mutually inconsistent, with one showing improved mood as a result of provocation (31), while the other shows worse mood (24). Meanwhile the cognitive effects of this last study were apparent in both the control group and the hypersensitive group and appeared to reflect both improvements and impairments in cognition (24). Twenty-four other blind or double-blind provocation studies have found no evidence that people with apparent EHS are especially sensible or hypersensitive to EMF. Our metaanalyses also confirmed these findings. In summary, we have therefore been unable to find any robust evidence to support the existence of EHS as a biologic entity.

On the other hand, several of the experiments reviewed also examined the effects of a nonblind exposure to the relevant stimulus (7,22,23). All found that when the participants were aware that the EMF source was switched on, they

TABLE 3. Provocation Studies for Generalized Electromagnetic Hypersensitivity.

Reference	Sample	Active Stimulus	Number and Length of Exposures	Results (all $p > .05$ unless otherwise indicated)		
				Total Number of Correct Discriminations Between Active and Sham (number of participants apparently demonstrating electromagnetic sensibility)	Type of Self-Reported Symptoms Measured and Comparison Between Active and Inactive Conditions	Other Health Outcomes Measured and Comparison Between Active and Inactive Conditions
Rea, 1991 (29)	100 EHS, 25 healthy controls	Exposure to EMFs of varying frequencies	Three testing phases involving repeated testing with 3-min exposures to different frequency EMFs and inactive challenges	EHS: not measured; control: not measured	Patients asked to describe any symptoms; 16/100 EHS participants consistently reported symptoms in active, but not inactive conditions, compared with 0/25 control participants	None
Wennberg, 1994 (32)	25 EHS, 13 healthy controls	ELF/VLF fields	Multiple exposures of less than 10 min	EHS: unreported (0/25); control: unreported (0/13)	Patient asked to report onset of any symptoms	None
Johansson, 1995 (33)	7 EHS	"Electric and/or magnetic fields"	Unknown number of 60-min provocations	Study abandoned; authors reported that "several milieu factors" may have interfered with the study	Not reported	Not reported
Wang, 1995 (30)	19 EHS, 34 healthy controls	Exposure to EMFs of varying frequencies	Nine 3-min provocations; 6 active, 3 inactive	Not measured	Unspecified symptoms	None
Bertoft, 1996 (34)	4 EHS	Exposure to EMFs generated by a dental chair and unit	Two 1-hr provocations; 1 active and 1 inactive	Not measured	Neurologic, musculoskeletal, cardiovascular, oral/respiratory, gastrointestinal, ocular, and dermal symptoms	None
Toomingas, 1996 (35)	1 EHS	Whole-body Helmholtz coil with 2 field intensities	Twenty-four 1 or 10-s provocations to inactive or active conditions	EHS: unreported (0/1)	Patient asked to describe any symptoms	None
Mueller, 2000 (31)	53 EHS	Exposure to intermittent or constant EMF	Exposure to active or inactive provocations (1 4-hr period per night for 25 nights) conducted while participant was sleeping	Not measured	Sleep quality, pleasure (p = .01), arousal (p = .05)	None
Reißenweber, 2000 (36)	37 EHS, 37 healthy controls	50-Hz sinusoidal field	Twenty 2-min exposures, half active, half inactive	EHS: unreported (unreported); control: unreported (unreported); authors report "no significant differences in guess probabilities of groups"	Patients asked to describe any symptoms, but no analyses reported	None
Lyskov, 2001 (37)	20 EHS, 20 healthy controls	Weak magnetic fields, with or without concurrent mathematical task	Two testing days: day 1 entirely inactive, day 2 had 4 10-min exposures to active and inactive fields, with or without maths task	EHS: unreported (0/20); control: unreported (0/20)	Tactile feelings and general fatigue more prevalent in inactive condition (no statistical analysis)	None.
Mueller, 2003 (38)	49 EHS, 14 healthy controls	Low-intensity EMF	Twenty 2-min provocations: 10 active and 10 inactive	EHS: unreported (6/49); control: unreported (1/14)	None	None

EHS = electromagnetic hypersensitivity; EMF = electromagnetic field.

TABLE 4. Other Provocation Studies

Reference	Sample	Active Stimulus	Number and Length of Exposures	Results (all $p > .05$ unless otherwise indicated)		
				Total Number of Correct Discriminations Between Active and Sham (number of participants apparently demonstrating electromagnetic sensibility)	Type of Self-Reported Symptoms Measured and Comparison Between Active and Inactive Conditions	Other Health Outcomes Measured and Comparison Between Active and Inactive Conditions
Trimmel, 1998 (39)	36 EHS, 30 healthy controls	EMFs generated by a transformer coil	Exposure to either 1 hr of EMF + noise or to 1 hr of just noise	Not measured	Discomfort	Unsuccessful visual processing, precise visual processing ($p < .05$), visual attention ($p < .05$), visual perception, verbal memory

EMF = electromagnetic field.

reported being able to detect the EMF or experienced more symptoms. Another study found that participants' beliefs about the status of a double-blind exposure significantly predicted symptom reporting regardless of whether these beliefs were correct (21). Given that the actual presence of EMF did not correlate with increased symptom severity in these studies, these findings suggest that psychologic mechanisms may play at least some role in causing or exacerbating EHS symptoms.

Review Methodology

Our results illustrate the need to conduct reviews systematically and without heed to the publication status, language, or conclusions of the primary research. By doing this, we have been able to identify a large number of studies that have gone unreported in previous reviews. It is always possible, however, that additional provocation studies exist that we were not able to find. Yet, given that publication bias makes studies with significant results easier to locate, it is very unlikely that any missing studies would alter our conclusions.

A subtler problem for this review concerns the homogeneity of the participants included in the original research. Although some studies focused on participants with a single complaint such as skin rashes caused by VDUs (17) or symptoms caused by mobile phones (28), others tested volunteers with more generalized and typically more severe sensitivities under the assumption that this would make any effect easier to detect (16). In this review, we have made no distinction between these categories. Given that there is no a priori reason to assume that any biophysical mechanisms governing the adverse effects of EMF will differ between these groups, we believe we are justified in doing this. Nevertheless, arguments might be made for assessing these groups independently. Although poor reporting by the original studies makes subdivision into these categories difficult (1), we do not believe that doing this would alter our conclusions; the studies reviewed provide no robust evidence for the existence of generalized EHS, and there is currently no good evidence for the existence of more specific sensitivities to mobile phone signals or VDU emissions. However, as new technologies with different EMF characteristics are developed, it is likely that new sensitivities to them will be reported. As such, there will always be room to argue that the latest form of EHS has yet to be fully investigated.

Research Methodology

Why have so many provocation studies failed to produce significant findings? A number of suggestions have been put forward. For example, it has been suggested (24,29) that only studies conducted in specially designed chambers, which shield against all extraneous background EMF, would be able to produce a significant result. However, although this would presumably reduce any "noise" in symptom reporting and make increased symptoms easier to identify, people with EHS do usually report being able to detect the presence of electromagnetic triggers in everyday life. It should therefore also be possible for scientists to detect this sensitivity against the

backdrop of normal EMF levels. Moreover, many of the studies reviewed did use techniques to reduce or control for background EMF but were still unable to identify an effect (7,12,16,19,21,28,30,36,38).

Other arguments sometimes heard are that the participants in an experiment were not sensitive enough, that the wrong symptoms were measured, that the exposure used was the wrong kind, or that the follow up was too short. Again, none of these seem very plausible as an explanation for all the negative results. In particular, we note that when provocation studies have included nonblind arms or training sessions, then it usually has been possible to measure an increase in symptoms (7,22,23). Other studies have found participants to be confident in their assertions that a particular session was active or inactive (15,21) or have identified increases in symptoms that are similar to those found after exposure to real-life triggers (18,34,37). The conclusions of the 1997 European Commission report thus still seem to be valid: participants do experience "realistic" symptoms in these experiments, but this is apparently not associated with the presence of EMF (1).

More of an issue are "hangover effects." EHS sufferers sometimes report symptoms that can last for several days (3). It is therefore important that studies use an appropriate interval between provocations to prevent symptoms experienced in one from masking any effects of the next. It is difficult to know how many studies were affected by this, but at least 2 reported that hangover effects did seem to have an impact on their results (18,29).

Low statistical power might also explain some of the negative findings. This is not simply an issue of sample size; testing a single participant numerous times can be a powerful design, although it does reduce the generalizability of any negative findings. Nevertheless, the majority of studies included relatively small sample sizes and failed to justify this by providing a power calculation. Such a calculation could be based on participant reports of usual symptom severity after real-life exposure to the stimulus and should now be given in any future research.

Implications for Researchers and Clinicians

We are aware of at least 6 more double-blind provocation studies into EHS that are currently ongoing, each of which is examining hypersensitivity symptoms associated with mobile phone-type signals. The results of these studies will determine whether any more research in this area is needed. If further studies are necessary, the following guidelines should be considered: 1) Studies should include a healthy control group. This will not only provide a standard against which to judge heightened sensibility (38), but it will also provide a useful indication of the adequacy of the blinding (16). 2) The nature and severity of participants' self-reported sensitivities should be assessed and reported. This might then be used to produce a power calculation, which should also be reported. 3) The inclusion of open-blind provocation sessions should be considered as a useful way of ensuring the face validity of the experiment. 4) Hangover effects should be controlled by the use of lengthy intervals between exposures or else checked for by the use of preexposure measures of symptom severity.

Our review suggests that treatment for EHS should not simply focus on reducing EMF exposure because this is unlikely to address the root causes of the problem (14). Identifying what these causes are may require careful investigation. For some, complaints of EHS may mask organic or psychiatric pathology, whereas others may benefit from a course of cognitive behavioral therapy (21).

CONCLUSIONS

This systematic review could find no robust evidence to support the existence of a biophysical hypersensitivity to EMF.

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REFERENCES

1. Bergqvist U, Vogel E, Aringer L, Cunningham J, Gobba F, Leitgeb N, Miro L, Neubauer G, Ruppe I, Vecchia P, Wadman C. Possible health implications of subjective symptoms and electromagnetic fields; a report prepared by a European group of experts for the European Commission, DG V. Solna: Arbete och Halsa; 1997.
2. Hillert L, Berglind N, Arnetz BB, Bellander T. Prevalence of self-reported hypersensitivity to electric or magnetic fields in a population-based questionnaire survey. Scand J Work Environ Health 2002;28: 33–41.
3. Röösli M, Moser M, Baldinini Y, Meier M, Braun-Fahrländer C. Symptoms of ill health ascribed to electromagnetic field exposure—a questionnaire survey. Int J Hyg Environ Health 2004;207:141–50.
4. Independent Expert Group on Mobile Phones. Mobile phone and health. Report of an independent expert group on mobile phones. Chilton: National Radiological Protection Board; 2000.
5. Ziskin MC. Electromagnetic hypersensitivity: a COMAR technical information statement. IEEE Eng Med Biol 2002;21:173–5.
6. Gangi S, Johansson O. A theoretical model based upon mast cells and histamine to explain the recently proclaimed sensitivity to electric and/or magnetic fields in humans. Med Hypotheses 2000;54:663–71.
7. Lonne-Rahm S, Andersson B, Melin L, Schultzberg M, Arnetz B, Berg M. Provocation with stress and electricity of patients with 'sensitivity to electricity.' J Occup Environ Med 2000;42:512–6.
8. Leitgeb N, Schröttner J. Electrosensibility and electromagnetic hypersensitivity. Bioelectromagnetics 2003;24:387–94.
9. Levallois P. Hypersensitivity of human subjects to environmental electric and magnetic field exposure: a review of the literature. Environ Health Perspect 2002;110(suppl 4):613–8.
10. Leitgeb N, Fluhr H. Einflussfaktoren der Elektrosensibilitat. VEO J 1998;6:44–50.
11. Skyberg K, Skulberg K, Eduard W, Vistnes AI, Levy F, Djupesland P. Electric fields, dust and health problems among VDU-users in an office environment. An intervention program. Advances Occup Ergonomics Safety 1998;2:81–3.
12. Sjöberg P, Hamnerius Y. Study of provoked hypersensitivity reactions from a VDU. In: Katjalainen, Knave B, eds. Electromagnetic Hypersensitivity. 2nd Copenhagen Conference; 1995.
13. Oftedal G, Vistnes AI, Rygge K. Skin symptoms after the reduction of electric fields from visual display units. Scand J Work Environ Health 1995;21:335–44.
14. Oftedal G, Nyvang A, Moen BE. Long-term effects on symptoms by reducing electric fields from visual display units. Scand J Work Environ Health 1999;25:415–21.

15. Keisu I.. Successful treatment of 'electricity hypersensitivity.' The patient was assisted in curing himself. [Swedish] Lakartidningen 1996;93: 1753–5.
16. Flodin U, Seneby A. Tegenfeldt C. Provocation of electric hypersensitivity under everyday conditions. Scand J Work Environ Health 2000; 26:93–8.
17. Nilsen A. Facial rash in visual display unit operators. Contact Dermatitis 1982;8:25–8.
18. Swanbeck G, Bleeker T. Skin problems from visual display units. provocation of skin symptoms under experimental conditions. Acta Derm Venereol 1989;69:46–51.
19. Hamnerius Y, Agrup G, Galt S, Nilsson R, Sandblom J, Lindgren R. Double-blind provocation study of hypersensitivity reactions associated with exposure from VDUs. Preliminary short version. R Swed Acad Sci Rep 1993;2:67–72.
20. Sandström M, Stenberg B, Hansson-Mild K. Experiences of provocations with electric and magnetic fields. R Swed Acad Sci Rep 1993;2:62–6.
21. Andersson B, Berg M, Arnetz BB, Melin L, Langlet I, Lidén S. A cognitive-behavioral treatment of patients suffering from 'electric hypersensitivity': subjective effects and reactions in a double-blind provocation study. J Occup Envion Med 1996;38:752–8.
22. Hellbom M. Provocation attempt with individuals hypersensitive to electricity. Effects of information about the presence of electric and magnetic fields. [Swedish Dissertation] Uppsala: Department of Applied Psychology, University of Uppsala; 1993.
23. Johansson O. Hypersensitivity to electricity and sensitivity to mobile phones. Results from a double-blind provocation study of methodological character [Swedish Report]. Stockholm: Department of Experimental Dermatology, Karolinska Institute; 1995.
24. Zwamborn APM, Vossen SHJA, van Leersum BJAM, Ouwens MA, Makel WN. Effects of global communication system radio-frequency fields of well being and cognitive functions of human subjects with and without subjective symptoms [Report]. The Hague: Netherlands Organisation for Applied Scientific Research (TNO); 2003.
25. Radon K, Maschke C. Hypersensitivity to electricity. [German] Umweltmedizin in Forschung und Praxis 1998;3:125–9.
26. Barth A, Maritczak L, Valic E, Konnaris C, Wolf C. Pseudoangina caused by exposure to electromagnetic fields ('electrosmog'). [German] Dtsch Med Wschr 2000;125:830–2.
27. Raczek J, Runow K, Oetzel H, Gailus T, Herget I. Investigations of electrosensitivity to a GSM signal at 900MHz for a self-reported electrosensitive target group. The Bioelectromagnetics Society 22nd Annual Meeting; 2000:269–70.
28. Hietanen M, Hämäläinen AM, Husman T. Hypersensitivity symptoms associated with exposure to cellular telephones: no causal link. Bioelectromagnetics 2002;23:264–70.
29. Rea WJ, Pan Y, Fenyves EJ, Sujisawa I, Samadi N, Ross GH. Electromagnetic field sensitivity. J Bioelectricity 1991;10:241–56.
30. Wang T. Sick building syndrome: a study of some contributing factors [Dissertation]. University of Surrey; 1995.
31. Mueller Ch H, Krueger H, Schierz Ch. Project NEMESIS: double-blind study on effects of 50Hz EMF on sleep quality and physiological parameters in people suffering from electrical hypersensitivity. The Bioelectromagnetics Society 22nd Annual Meeting; 2000:89–90.
32. Wennberg A, Franzén O, Paulsson L-E. Electromagnetic field provocations of subjects with 'electric hypersensitivity.' In: Simunic D, ed. COST 244 meeting on Electromagnetic Hypersensitivity. Graz: COST 244; 1994:133–9.
33. Johansson O, Liu P-Y. 'Electrosensitivity,' 'electrosupersensitivity' and 'screen dermatitis': preliminary observations from on-going studies in the human skin. In: Simunic D, ed. Proceedings of Cost 244: Biochemical effects of electromagnetic fields—workshop on electromagnetic hypersensitivity. Graz: EU (DG XIII); 1995:52–7.
34. Bertoft G. Patient reactions to some electromagnetic fields from dental chair and unit: a pilot study. Swed Dent J 1996;20:107–12.
35. Toomingas A. Provocation of the electromagnetic distress syndrome. Scand J Work Environ Health 1997;22:457–8.
36. Reißenweber J, David E, Kentner S. Different aspects of electromagnetic hypersensitivity. The Bioelectromagnetics Society 22nd Annual Meeting; 2000:270–1.
37. Lyskov E, Sandstrom M, Hansson Mild K. Provocation study of persons with perceived electrical hypersensitivity and controls using magnetic field exposure and recording of electrophysiological characteristics. Bioelectromagnetics 2001;22:457–62.
38. Mueller CH, Krueger H, Schierz C. Project NEMESIS: perception of a 50 Hz electric and magnetic field at low intensities (laboratory experiment). Bioelectromagnetics 2002;23:26–36.
39. Trimmel M, Schweiger E. Effects of an ELF (50 Hz, 1 mT) electromagnetic field (EMF) on concentration in visual attention, perception and memory including effects of EMF sensitivity. Toxicol Lett 1998;96–97: 377–82.

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Research

Are some people sensitive to mobile phone signals? Within participants double blind randomised provocation study

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Abstract

Objective To test whether people who report being sensitive to mobile phone signals have more symptoms when exposed to a pulsing mobile signal than when exposed to a sham signal or a non-pulsing signal.

Design Double blind, randomised, within participants provocation study.

Setting Dedicated suite of offices at King's College London, between September 2003 and June 2005.

Participants 60 "sensitive" people who reported often getting headache-like symptoms within 20 minutes of using a global system for mobile communication (GSM) mobile phone and 60 "control" participants who did not report any such symptoms.

Intervention Participants were exposed to three conditions: a 900 MHz GSM mobile phone signal, a non-pulsing carrier wave signal, and a sham condition with no signal present. Each exposure lasted for 50 minutes.

Main outcome measures The principal outcome measure was headache severity assessed with a 0-100 visual analogue scale. Other outcomes included six other subjective symptoms and participants' ability to judge whether a signal was present.

Results Headache severity increased during exposure and decreased immediately afterwards. However, no strong evidence was found of any difference between the conditions in terms of symptom severity. Nor did evidence of any differential effect of condition between the two groups exist. The proportion of sensitive participants who believed a signal was present during GSM exposure (60%) was similar to the proportion who believed one was present during sham exposure (63%).

Conclusions No evidence was found to indicate that people with self reported sensitivity to mobile phone signals are able to detect such signals or that they react to them with increased symptom severity. As sham exposure was sufficient to trigger severe symptoms in some participants, psychological factors may have an important role in causing this condition.

Trial registration ISRCTN81432775.

Introduction

The recent uptake of mobile phones has been accompanied by some concern about possible health risks.[1] In the general population, the health effects most often attributed to mobile phone use are non-specific symptoms. Excluding sensations of mild warmth, the most commonly reported symptoms are headache, burning, dizziness, fatigue, and tingling.[2] Mechanisms to explain these phenomena remain speculative, and although the pulsing nature of "global system for mobile communication" (GSM) signals has been suggested to be partly to blame,[3] experiments that have exposed healthy adults to GSM signals under blind conditions have not found any significant effects on the reporting of symptoms.[4]

Whether a subgroup of people who are more sensitive to GSM exists remains unclear. Of particular interest are people who report symptoms almost every time they use a mobile phone.[5] This phenomenon falls within the broader category of "electromagnetic sensitivity," a medically unexplained condition in which non-specific symptoms are reported after perceived exposure to any of a wide range of electrical devices, including mobile phones, visual display units, and power lines. The prevalence of self reported electromagnetic sensitivity in the United Kingdom is unknown, but community studies in Sweden and California put the figure at between 1.5% and 3%.[6,7] Provocation studies that have exposed people who report electromagnetic sensitivity to electromagnetic fields under blind conditions have so far failed to provide any good evidence linking the presence of electromagnetic fields to severity of symptoms.[8] Several authors have therefore suggested that psychological mechanisms may be more relevant in causing the condition.[9]

We tested whether people with self reported sensitivity to GSM would experience greater headache severity after double blind exposure to a GSM signal than after exposure to a sham signal. Secondary outcomes included other symptoms and ability to discriminate GSM from sham signals. We also tested whether a pulsing signal resulted in greater reporting of symptoms than a non-pulsing signal.

Methods

Study design

In this within participants study, we exposed people who reported adverse reactions to mobile phone signals (sensitive group) or who did not report any such effects (control group) to three conditions: a signal mimicking that produced by a 900 MHz GSM mobile phone, an unpulsed continuous wave signal, and a sham exposure with no signal present. Our Clinical Trials Unit determined the order in which these conditions occurred for each participant on enrolment, by using a computerised random numbers generator and counter-balancing within blocks of six consecutive participants.

Exposures were double blind—that is, neither participants nor researchers were told which type of exposure was present in which testing session. The controls for our exposure equipment allowed for 256 possible settings, of which 15 had been randomly allocated to each condition. Only the Clinical Trials Unit knew which settings related to which exposure. For the first nine control participants and six sensitive participants (11.5% of all participants), Clinical Trials Unit staff told researchers which

setting to use on the morning of each exposure. Given the theoretical possibility that the meaning of a setting might eventually be inferred by observing several participants' reactions to it, for the remaining sessions Clinical Trials Unit staff entered the codes and then obscured them from the researchers with opaque tape.

Participants

To be eligible for the sensitive group, participants had to report often experiencing headache-like symptoms within 20 minutes of using a 900 MHz GSM mobile phone. Participants who did not attribute any symptoms to mobile phone signals were eligible for the control group. We excluded people who were aged under 18 or over 75, were pregnant, had a psychotic illness, were currently using antidepressants, or reported severe symptoms at baseline while in our testing room. We recruited participants through mailshots organised by an electromagnetic sensitivity support group, advertising by interested clinicians and by our funding body, posters in general practitioners' surgeries, adverts and articles in the press and specialist health publications, email circulars, and word of mouth.

Exposures

We generated exposures by using the standard GSM handset system used within the UK Mobile Telecommunications and Health Research programme.[10] The antenna for this headband mounted system was positioned slightly above and behind the left ear and within a few millimetres of the participant's scalp. Both GSM and continuous wave conditions produced a target specific absorption rate adjacent to the antenna of 1.4 W/kg, with an uncertainty of ±30%. For the sham exposure, a continuous wave signal was generated to ensure that the system heated up to the same degree as the active exposures but was diverted to an internal load instead of being transmitted through the antenna; only minimal leakage of this signal occurred (specific absorption rate <0.002 W/kg).

Questionnaires

We assessed severity of symptoms during exposure by using 100 mm visual analogue scales,[11] anchored with the phrases "no sensation" and "worst possible sensation." These scales measured headaches; nausea; fatigue; dizziness; skin itching, tingling, or stinging; sensations of warmth or burning on skin; and eye pain or dryness.

We collected other data at baseline, consisting of demographics and current or previous mobile phone usage. We also asked participants to record the frequency with which they experienced 11 common symptoms after a mobile phone call (never, 25% of calls, 50% of calls, 75% of calls, every call). We asked participants in the sensitive group about duration of illness and symptoms, how near a mobile phone needed to be before they could detect it, whether they considered themselves to have "electrosensitivity or sensitivity to electromagnetic fields," whether they had sought treatment, and whether their sensitivity impaired their daily functioning.[12]

Procedure

We sent written information to people who contacted us and screened them for eligibility. We invited those who provided verbal consent to attend our unit for three mornings. We instructed participants not to take recreational drugs for one week before attending; not to drink alcohol for 24 hours beforehand; and not to drink more than one cup of tea or coffee, take painkillers, or undertake strenuous physical activity or anything psychologically stressful on the morning of each visit.

Sessions began with a 30 minute adjustment period. During this time in session one, participants provided informed written consent and completed the various demographic questionnaires. At the end of these adjustment periods, we asked participants to complete baseline visual analogue scale measures. The exposure equipment was then attached and switched on for 50 minutes. Participants completed further visual analogue scale measures after 5, 15, 30, and 50 minutes. If a participant requested that an exposure be terminated early, visual analogue scales were administered immediately. All participants completed a final set of visual analogue scales 30 minutes after the end of each exposure. At this point we asked them to state whether they believed a signal had been present and their confidence about this (100 mm visual analogue scales from "complete guess" to "100% certain"). At least 24 hours after each session we contacted participants and asked them whether they had experienced any visual analogue scale symptoms in the 24 hours since exposure. We ascertained a score of 0 (no sensation) to 10 (worst possible sensation) for any symptoms that were reported, and we categorised participants scoring 5 or more as having experienced a "definite" symptom.

All testing took place between September 2003 and June 2005 in two rooms within King's College London. The rooms, which were lit by two table lamps, were not shielded against outside electromagnetic fields.

Sample size calculation

We based our sample size calculation on our ability to detect a change in headache severity within the sensitive group after 50 minutes of GSM exposure, using a two way analysis of variance with one between participants factor (sensitive *v* control) and one within participants factor (GSM *v* continuous wave *v* sham). On the basis of previous studies in healthy and electrosensitive participants,[1 13] this analysis assumed that control participants would report a mean headache severity of 10 units in all three experimental conditions whereas sensitive participants would report a mean severity of 11.7 in the sham and continuous wave conditions, with standard deviations of 26.8. In the absence of any pre-existing data, we assumed correlations of $r=0.5$ between conditions and that any effect of GSM in the sensitive group would be moderate—that is, an effect size of 0.5. Our calculation showed that to detect this effect as significant at the 5% level and with 80% power we would need 60 participants in each group. In practice, although these assumptions turned out to be reasonable, the nature of our data required us to adopt a different analytical strategy from that originally planned. As such, this calculation should be taken as indicative only.

Analyses

To analyse symptom severity over time, we used generalised estimating equations.[14] This approach was needed to accommodate the extremely positively skewed distribution of each response variable and to allow the inclusion of a suitable correlation structure for the repeated measures of each response. These models also allowed us to take into account differing lengths of exposure for participants who requested that an exposure be terminated early. The specific generalised estimating equations model fitted to each response used log(symptom severity+1) as the dependent variable, a gamma error distribution, and an exchangeable correlation structure. We used robust standard errors to judge the "significance" or otherwise of the explanatory variables included in the fitted models.[15]

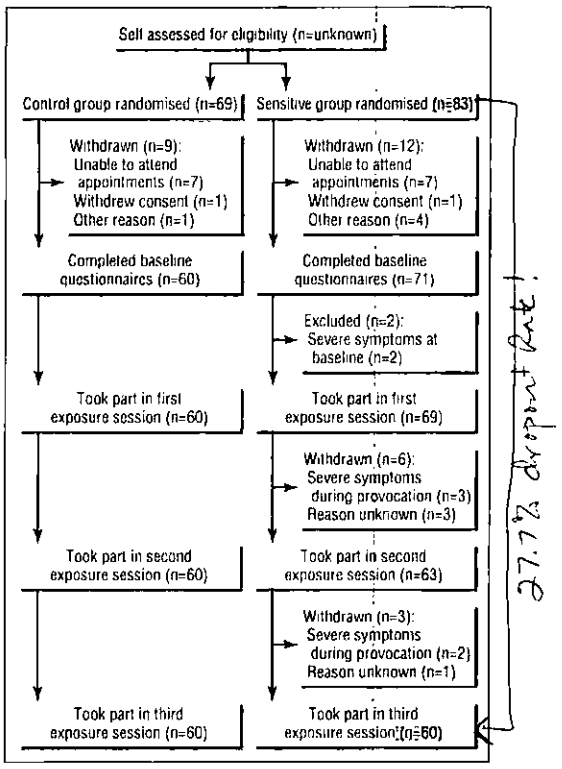

Fig 1 Study flow diagram

Results

We were contacted by 83 potential sensitive participants and 69 potential controls who met the inclusion criteria and provided verbal consent. Of these, 71 sensitive participants and 60 controls attended for their first testing session, and 60 in each group attended all three testing sessions and were included in our main generalised estimating equations analyses (fig 1). Table 1 shows demographic data for those participants who attended at least one session; the only substantive difference between the groups was a significantly higher proportion of sensitive participants from a professional or managerial background ($\chi^2 = 5.6$, $P = 0.02$). Restricting the demographic comparisons to participants who completed all three testing sessions did not alter these results.

For sensitive participants, the mean reported delay between beginning a call and onset of symptoms in everyday life was 6.5 (SD 6.5) minutes. For 48 people, symptoms usually resolved within two hours. All but one had been sensitive for at least a year (median 4 (interquartile range 2-5) years). Eighteen people reported that their sensitivity to mobile phones caused "definite" impairment or worse in at least one aspect of daily functioning, and 15 people reported having sought treatment for their condition. Thirteen people reported being sensitive to mobile phones at distances of one metre or more, and the same number reported having "electrosensitivity." Sensitive participants reported headache-like symptoms in a mean of 70.4% of calls. The next most common symptoms were skin warmth or burning (43.8% of calls), difficulty concentrating (30.0%), and dizziness (20.8%). Very few control participants reported any symptoms in relation to mobile phone signals; the highest mean frequency was for skin warmth or burning (2.9%).

Table 1 Demographics of participants

Variable	Control group (n=60)	Sensitive group (n=71)	P value for differences between groups
Mean (SD) age (years)	33.5 (10.2)	37.1 (13.2)	0.09
Sex (male:female)	27:33	31:40	0.88
Ethnicity (white:other)	45:15	56:15	0.60
Marital status (single:married/cohabiting:divorced/separated)	39:19:2	38:30:3	0.41
Employment status (in work:unemployed:housewife/husband:student)	30:10:2:18	42:9:3:17	0.71
Socioeconomic status (professional, managerial, or intermediate:semiroutine, routine, or student)	31:29	51:20	0.02
Educational level (secondary education or lower:higher education)	18:42	26:45	0.42
Weekly frequency of mobile phone use (<4 times:4-12 times:13+ times)*	8:25:27	17:22:32	0.23
Typical length of call (<5 minutes:5-15 minutes:16+ minutes)*	32:22:6	44:18:9	0.37

*Former mobile users (n=10) based their answers on the last time they regularly used one.

Table 2 shows the results of fitting generalised estimating equation models to each response variable. The group×time interaction term was not needed in any model, so it does not appear in this table. Fitted models for all response variables showed highly significant effects for time (both linear and quadratic effects) and for baseline severity. We found no convincing evidence of an effect of condition or a condition×group effect for any of the symptoms. For headache, burning sensations, skin sensations, and eye pain we found evidence of a main group effect—sensitive participants reported greater severity. In terms of the original visual analogue scale units, this group effect for headache severity equated to an increase of 1.0 (95% confidence interval 0.4 to 2.0) unit. Figure 2 shows the median headache severity by group for each exposure condition, and figure 3 illustrates the main effect of group on headache severity collapsed across conditions.

We also analysed the number of severe reactions seen in each condition, with a severe reaction defined as a participant requesting that an exposure be terminated early or withdrawing from the study entirely after an exposure. Twenty six such reactions occurred in the sensitive group (9 withdrawals; 17 early terminations), and none occurred in the control group. These reactions were equally distributed between GSM (n = 7), continuous wave (n = 10), and sham (n = 9) conditions ($\chi^2 = 0.54$, $P = 0.76$). Excluding data relating to the four participants whose reasons for withdrawal were not explicitly stated to us (see fig 1) did not affect these results (GSM 5, continuous wave 9, sham 8; $\chi^2 = 1.2$, $P = 0.55$).

We had next day follow-up results for all three sessions for 41 control participants and 49 sensitive participants. Cochran's Q tests identified no significant differences in the number reporting at least one definite symptom after GSM, continuous wave, or sham exposures in either the control group (GSM 0/41, continuous wave 2/41, sham 1/41; $Q = 4.0$, $P = 0.14$) or the sensitive group (GSM 5/49, continuous wave 8/49, sham 4/49; $Q = 2.0$, $P = 0.37$).

Table 3 shows participants' assessments of whether a signal was present during provocation. The proportion who believed a signal was present during exposure to GSM (60% of sensitive participants, 58% of controls) was slightly less than for the sham

Table 2 Estimated regression coefficients (robust standard error) derived from generalised estimating equation models used to assess effects of group, exposure, duration of exposure, and baseline score on symptom severity

Symptom	Baseline severity	Duration (linear function)	Duration (quadratic function)	Sensitive *v* control	Sham *v* GSM	CW *v* GSM	Group x (sham *v* GSM)	Group x (CW *v* GSM)
Headache	0.04 (0.008)	0.04 (0.004)	−0.0004 (0.0004)	0.7 (0.2)	0.07 (0.1)	−0.02 (0.1)	−0.08 (0.2)	0.2 (0.2)
Nausea	0.02 (0.05)	0.006 (0.001)	−0.0002 (0.00004)	0.2 (0.3)	0.06 (0.1)	−0.2 (0.1)	0.1 (0.4)	0.3 (0.3)
Fatigue	0.04 (0.005)	0.01 (0.002)	−0.0003 (0.00005)	0.2 (0.2)	−0.08 (0.1)	−0.2 (0.1)	−0.09 (0.2)	0.2 (0.2)
Dizziness	0.05 (0.02)	0.007 (0.001)	−0.0003 (0.00005)	0.3 (0.2)	−0.2 (0.1)	−0.09 (0.1)	0.2 (0.3)	−0.01 (0.3)
Skin	0.05 (0.01)	0.004 (0.001)	−0.0003 (0.00005)	0.5 (0.2)	−0.09 (0.1)	−0.1 (0.1)	0.1 (0.2)	0.3 (0.2)
Burning	0.03 (0.00005)	0.007 (0.001)	−0.0007 (0.0004)	0.4 (0.2)	−0.05 (0.1)	−0.09 (0.09)	0.2 (0.2)	0.4 (0.2)
Eye pain	0.05 (0.008)	0.007 (0.001)	−0.0003 (0.00004)	0.6 (0.2)	−0.04 (0.1)	0.2 (0.1)	−0.3 (0.2)	−0.08 (0.2)

CW=continuous wave; GSM=global system for mobile communication.
In each model, the dependent variable used was log(symptom severity +1).

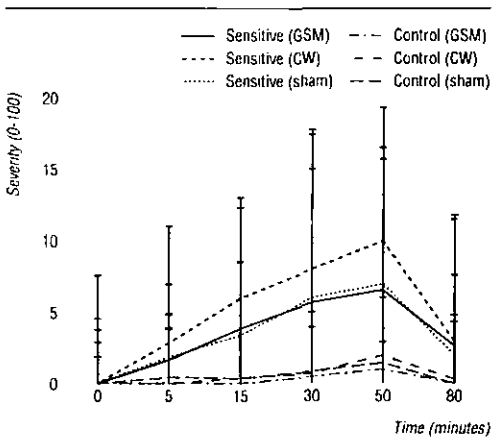

Fig 2 Median headache severity (error bars show interquartile range) during provocation with global system for mobile communication (GSM), continuous wave (CW), and sham exposures for sensitive and control participants. For clarity, graph does not include data relating to exposures that were terminated early, although these data were included in analyses

exposure (63% of sensitive participants, 68% of controls). Self reported confidence for these judgments did not differ greatly (table 3).

Discussion

We found no evidence to indicate that self reported sensitivity to 900 MHz GSM mobile phone signals has a biological basis. Nor did we find any evidence to suggest that the pulsing nature of GSM contributes to these symptoms. These findings agree with the large majority of previous blind or double blind provocation studies for electromagnetic sensitivity, which have found no differences in the severity of symptoms elicited by active or sham exposure to electromagnetic fields.[5]

Did some inadequacy exist in our methods that might account for these "negative" findings? If it did, we are unaware of it. The exposure represented a relatively "worst case scenario" mobile phone call, using a high specific absorption rate and lasting almost eight times longer than the mean call length usually needed to trigger symptoms in our sensitive sample. Interference from participants' reactions to extraneous electromagnetic fields is also unlikely: after 30 minutes adjusting to our offices, only two

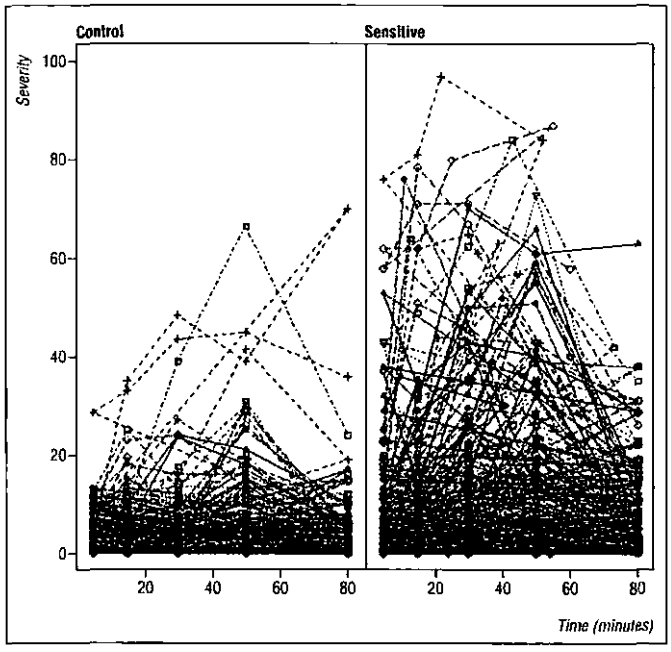

Fig 3 Headache severity over time for each participant, illustrating main effect of group on severity. Data for this figure have been collapsed across all three exposure conditions

Table 3 Number of participants who believed a signal was present for each experimental condition and mean (SD) confidence (0-100) reported by participants for these "signal present" assessments

Exposure	Controls		Sensitive participants			
			Completed all three exposures		Completed at least one exposure	
	No	Confidence	No	Confidence	No	Confidence
GSM	35/60	36.8 (28.5)	36/60	58.6 (30.8)	41/65	61.2 (31.0)
CW	42/60	39.7 (33.0)	41/60	57.7 (27.8)	45/64	57.8 (28.9)
Sham	41/60	43.9 (31.9)	38/60	64.4 (31.7)	39/63	64.0 (31.3)

CW=continuous wave; GSM=global system for mobile communication.

participants reported baseline symptoms that might have masked any effects of exposure, and both were excluded. Finally, as we were able to detect changes in symptom severity over time as highly significant, the sensitivity of our visual analogue scales and our statistical techniques do not seem to have had any shortcomings.

That symptom severity did increase during exposure is interesting. These symptoms were not trivial. Indeed, for some they were so severe that exposures had to be stopped early or the participants withdrew from the study. The confidence that sensitive participants had in their ability to discriminate active from sham signals also suggests that they experienced reactions similar to those encountered in real life, a finding also reported in previous provocation studies.[8] That apparently realistic symptoms can be induced in provocation experiments, despite no differences being observed between active and sham conditions, suggests that the acute symptoms reported by sensitive people in everyday life may be the result of a nocebo phenomenon. Such phenomena have previously been observed in relation to a wide range of stimuli,[15] including headaches induced by providing misleading information about the presence of electrical fields.[16] The mechanisms governing nocebo effects need further study but seem to include conscious expectation of symptoms and the presence of negative affect,[17 18] factors that are likely to be present whenever people who perceive themselves to be sensitive to mobile phones have to make use of the technology.

In terms of their clinical implications, these results do not suggest that attempting to reduce exposure to mobile phone signals will be a useful strategy for patients who report sensitivity to them. Although such interventions might be actively sought by patients and may even produce a short term reduction in symptoms mediated by a placebo effect,[19] in the longer term a danger exists that they will reinforce a patient's view of himself or herself as being sensitive to electromagnetic fields and put him or her at risk of developing symptoms associated with other electrical stimuli. Instead, it may be better to encourage such patients to test alternative non-electromagnetic field related explanations for their symptoms by using principles derived from cognitive behavioural therapy.[9]

We thank everybody who participated in this study, especially those in the sensitive group. We also thank Phil Chadwick from MCL-UK for supplying and calibrating the exposure equipment, and the staff from the Mental Health and Neurology Clinical Trials Unit at the Institute of Psychiatry for doing the randomisation and double blinding of the study.

Contributors: GJR had the original idea for the study and developed the study design with AJC, GH, and SW. GH and GJR did the testing. BSE analysed the symptom severity data; GJR did all other analyses. GJR wrote the first draft of the paper, and all authors contributed to further drafts. SW is the guarantor.

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Competing interests: None declared.

Ethical approval: The South London and Maudsley NHS Trust Research Ethics Committee granted approval for the study.

1 National Radiological Protection Board. Mobile phones and health 2004: report by the board of the NRPB. *Documents of the NRPB* 2004;15.
2 Oftedal G, Wilen J, Sandstrom M, Mild KH. Symptoms experienced in connection with mobile phone use. *Occup Med* 2000;50:237-45.
3 Hyland GJ. Physics and biology of mobile telephony. *Lancet* 2000;356:1833-6
4 Koivisto M, Haarala C, Krause CM, Revonsuo A, Laine M, Hamalainen H. GSM phone signal does not produce subjective symptoms. *Bioelectromagnetics* 2001;22:212-5.
5 Hocking B. Preliminary report: symptoms associated with mobile phone use. *Occup Med* 1998;48:357-60.
6 Hillert L, Berglind N, Arnetz BB, Bellander T. Prevalence of self-reported hypersensitivity to electric or magnetic fields in a population-based questionnaire survey. *Scand J Work Environ Health* 2002;28:33-41.
7 Levallois P, Neutra R, Lee G, Hristova L. Study of self-reported hypersensitivity to electromagnetic fields in California. *Environ Health Perspect* 2002;110(suppl 4):619-23.
8 Rubin GJ, Das Munshi J, Wessely S. Electromagnetic hypersensitivity: a systematic review of provocation studies. *Psychosom Med* 2005;67:224-32.
9 Rubin G, Das Munshi J, Wessely S. A systematic review of treatments for electromagnetic hypersensitivity. *Psychother Psychosom* 2006;75:12-8
10 MCL MTHR GSM and TETRA handset exposure systems for human volunteer studies. www.mcluk.org/MTHR_exposure_systems (accessed 23 Dec 2005)
11 McDowell I, Newell C. Visual analogue pain rating scales. In: McDowell I, Newell C, eds. *Measuring health: a guide to rating scales and questionnaires*. Oxford: Oxford University Press, 1996:341-6
12 Mundt JC, Marks IM, Shear MK, Greist JH. The work and social adjustment scale: a simple measure of impairment in functioning. *Br J Psychiatry* 2002;180:461-4.
13 Andersson B, Berg M, Arnetz BB, Melin L, Langlet I, Liden S. A cognitive-behavioral treatment of patients suffering from 'electric hypersensitivity': subjective effects and reactions in a double-blind provocation study. *J Occup Environ Med* 1996;38:752-8.

What is already known on this topic

Non-specific symptoms such as headaches, tingling sensations, and fatigue are sometimes attributed to mobile phone use

No generally accepted mechanisms exist that might explain how mobile phone signals could cause such effects

A minority of people also report being particularly sensitive to mobile phones, experiencing symptoms almost every time they use one

What this study adds

The signals produced by 900 MHz GSM mobile phones do not cause greater subjective symptoms than sham exposures in which no signal is present, even in people who report sensitivity to mobile phones

The symptoms reported by "sensitive" people may be the result of a nocebo effect and may be primarily psychological in origin

14 Everitt B *Modern medical statistics*. London: Arnold, 2003.
15 Barsky AJ, Saintfort R, Rogers MP, Borus JF. Nonspecific medication side effects and the nocebo phenomenon. *JAMA* 2002;287:622-7.
16 Schweiger A, Parducci A. Nocebo: the psychologic induction of pain. *Pavlov J Biol Sci* 1981;16:140-8.
17 Benedetti F, Pollo A, Lopiano L, Lanotte M, Vighetti S, Rainero I. Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. *J Neurosci* 2003;23:4315-23.
18 Petrie KJ, Moss-Morris R, Grey G, Shaw M. The relationship of negative affect and perceived sensitivity to symptom reporting following vaccination. *Br J Health Psychol* 2004;9:101-11.
19 Oftedal G, Nyvang A, Moen BE. Long-term effects on symptoms by reducing electric fields from visual display units. *Scand J Work Environ Health* 1999;25:415-21.

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Review

Idiopathic Environmental Intolerance Attributed to Electromagnetic Fields (Formerly 'Electromagnetic Hypersensitivity'): An Updated Systematic Review of Provocation Studies

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Idiopathic Environmental Intolerance attributed to electromagnetic fields (IEI-EMF; formerly 'electromagetic hypersensitivity') is a medically unexplained illness in which subjective symptoms are reported following exposure to electrical devices. In an earlier systematic review, we reported data from 31 blind provocation studies which had exposed IEI-EMF volunteers to active or sham electromagnetic fields and assessed whether volunteers could detect these fields or whether they reported worse symptoms when exposed to them. In this article, we report an update to that review. An extensive literature search identified 15 new experiments. Including studies reported in our earlier review, 46 blind or double-blind provocation studies in all, involving 1175 IEI-EMF volunteers, have tested whether exposure to electromagnetic fields is responsible for triggering symptoms in IEI-EMF. No robust evidence could be found to support this theory. However, the studies included in the review did support the role of the nocebo effect in triggering acute symptoms in IEI-EMF sufferers. Despite the conviction of IEI-EMF sufferers that their symptoms are triggered by exposure to electromagnetic fields, repeated experiments have been unable to replicate this phenomenon under controlled conditions. A narrow focus by clinicians or policy makers on bioelectromagnetic mechanisms is therefore, unlikely to help IEI-EMF patients in the long-term. Bioelectromagnetics 31:1–11, 2010. © 2009 Wiley-Liss, Inc.

Key words: environmental illness; electromagnetic fields; somatoform disorders; environmental exposure; cellular phone

INTRODUCTION

In recent years, many parts of the world have witnessed social and political controversies surrounding the introduction of new electrical technologies, particularly technologies which involve the transmission of digital radiofrequency fields. Despite the lack of any clear-cut evidence demonstrating that these technologies have adverse health effects and the lack of any generally accepted mechanism through which these effects could occur [Scientific Committee on Emerging and Newly Identified Health Risks, 2009], innumerable media stories about the potential effects of mobile phones, mobile phone base stations, wireless computer systems, digital baby monitors and the like, have left the public feeling uncertain and anxious. This anxiety has been further exacerbated by the precautionary advice given out by some governmental organisations concerning the appropriate use of these technologies [Barnett et al., 2008].

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Both media stories and the continuing provision of precautionary advice have been partially driven by the existence of people who claim to have detected a clear link between their own poor health and exposure to a specific electrical device [Burgess, 2004; Goldacre, 2007; Stewart, 2008]. Their condition, often described as either 'electromagnetic hypersensitivity' or 'electrosensitivity', manifests itself as the occurrence of subjective symptoms which the individual attributes to the presence of man-made electromagnetic fields. This condition can have major implications for a person's quality of life and is associated with decrements in general health status, increased levels of distress, increased levels of health service use, and impairments in occupational and social functioning [Roosli et al., 2004; Carlsson et al., 2005; Rubin et al., 2007]. The condition is also notable for its heterogeneity: no consistent pattern has been detected in the type of symptoms reported by sufferers [Hillert et al., 2002; Levallois et al., 2002; Roosli et al., 2004], the speed in which these symptoms develop following exposure [Roosli et al., 2004] or the types of electromagnetic exposure which apparently trigger the symptoms [Roosli et al., 2004]. Even the prevalence of the condition is heterogenous: while some areas such as California and Sweden have prevalence rates of 3.2% and 1.5%, respectively [Hillert et al., 2002; Levallois et al., 2002], over 10% of Germans attribute adverse health effects to mobile phone base stations [Blettner et al., 2009] while other countries, such as Iran, apparently have few, if any, sufferers [Mortazavi et al., 2007].

The aetiology of 'electromagnetic hypersensitivity' is controversial. While most patients and some scientists believe that the condition is caused by an as yet unrecognised 'bioelectromagnetic' mechanism, most mainstream medical bodies maintain that there is not sufficient evidence to support this theory and that the symptoms experienced by sufferers are unrelated to the presence of electromagnetic fields. Indeed, a working group of the World Health Organisation has recommended that the use of terms like 'electromagnetic hypersensitivity' should be discontinued in favour of the more aetiologically neutral phrase 'idiopathic environmental intolerance attributed to electromagnetic fields (IEI-EMF)' [Hillert et al., 2006]. Resolving this aetiological debate is an important task, not least because these two opposing theories have different implications in terms of identifying the most appropriate treatment [Rubin et al., 2006a].

One powerful technique for testing the role of electromagnetic fields in triggering IEI-EMF symptoms is the double-blind experimental provocation study, in which volunteers are exposed to active and sham electromagnetic fields under controlled conditions. In 2005, we reported a systematic review of all provocation studies for IEI-EMF published up to January 2004 [Rubin et al., 2005]. Of the 31 studies located, only 7 reported any significant effect of exposure on symptom severity. Of these, three had important shortcomings in their statistical methods, two could not be subsequently replicated by the same research teams and the final two produced contradictory results. Our conclusion was that 'we have therefore been unable to find any robust evidence to support the existence of (electromagnetic hypersensitivity) as a biologic entity.' In this article we report an update to that review. Our goals remained to test whether people who have IEI-EMF are better at detecting electromagnetic fields under blind conditions than people without IEI-EMF, and to test whether they respond to the presence of weak electromagnetic fields with increased symptom reporting.

METHODS

Search Strategy for the Identification of New Studies

We searched the following electronic databases for articles that included IEI-EMF-related keywords (e.g., 'electrosensitivity', 'environmental intolerance', 'electrosmog'): AMED, Embase, Medline, Psychinfo, Scopus, Web of Knowledge, the WHO EMF research database, the EMF-Portal database, WorldCatDissertations, and the Networked Digital Library of Theses and Dissertations. Four databases (AMED, Embase, Medline and Psychinfo) were also searched for articles which included combinations of stimulus and symptom keywords (e.g., 'mobile phone' and 'headache'). In addition, citation analyses were conducted for two review articles published on this topic in 2005 [Rubin et al., 2005; Seitz et al., 2005]; the journal Bioelectromagnetics was hand-searched and also conference proceedings from the Bioelectromagnetics Society; and the reference sections of the included articles were examined. All sources were checked for articles published between January 2004 and November 2008. Articles were initially screened by checking their titles and abstracts online. The full texts of any that appeared relevant were then obtained for a more detailed review.

Inclusion Criteria

The same inclusion criteria used in our original review were applied [Rubin et al., 2005]. In brief, studies were included only if they: tested a discrete sample of participants who reported experiencing subjective symptoms which they associated with

common electrical devices; experimentally exposed those participants to at least two conditions involving different levels of electromagnetic fields; performed this exposure blind or double-blind; and either assessed levels of subjective symptoms following each exposure or assessed participants' abilities to discriminate between the experimental conditions. Studies that tested only 'healthy' participants who did not report IEI-EMF were excluded from the review.

Data Extraction

For each study we extracted data on the number of participants, type of exposures and results for any statistical tests, based on symptom severity or ability to discriminate between conditions. As IEI-EMF is defined solely in terms of an apparent relationship between subjective symptoms and electromagnetic fields, we did not extract data about any outcomes which were not directly related to self-reported symptoms or the ability to perceive electromagnetic fields. For example, we did not extract data concerning EEG measurements, blood chemistry results or objectively measured cognitive function.

Review Process

The initial search for articles was conducted by GJR. The application of the inclusion criteria and data extraction were conducted independently by GJR and RNH with any disparities resolved through discussion.

RESULTS

Search Results

In total, the searches retrieved 2093 citations. Of these, 77 articles appeared potentially relevant to the review and were examined in full. Sixteen articles detailing 17 experiments involving 487 IEI-EMF participants were included in the update. One of these, David et al. [2006], was a report about an experiment that was included in our previous review article [Reissenweber et al., 2000]. This new article was, nevertheless, included in the update because it described the results from a larger sample of IEI-EMF participants than had been previously reported. Taking this overlap into account and combining the update with our earlier review identified a total of 46 provocation studies for IEI-EMF that tested 1175 participants with the condition.

Of the 16 experiments included in the update, seven involved exposure to a signal designed to emulate a mobile phone handset [Wilen et al., 2006; Rubin et al., 2006b; Oftedal et al., 2007; Bamiou et al., 2008; Hillert et al., 2008; Kim et al., 2008; Kwon et al., 2008], four tested the effects of exposure to mobile phone base station-type signals [Regel et al., 2006; Eltiti et al., 2007; Augner et al., 2009; Furubayashi et al., 2009], four involved exposure to magnetic fields generated using transcranial magnetic stimuli or other magnetic coils [Frick et al., 2005; Wenzel et al., 2005; David et al., 2006; Landgrebe et al., 2008b] and one assessed the effects of installing a protective Faraday cage over the beds of IEI-EMF sufferers [Leitgeb et al., 2008].

Mobile Phone Handset Experiments

Table 1 shows the results for the mobile phone handset-related experiments. No significant effect of exposure was reported in five of these studies [Wilen et al., 2006; Rubin et al., 2006b; Oftedal et al., 2007; Bamiou et al., 2008; Kwon et al., 2008]. In one study, a significant increase in headache severity was detected after 2¾ h exposure [Hillert et al., 2008], however this effect was attributable to an increase in the healthy control group rather than the IEI-EMF group [Hillert et al., 2008]. This same study also reported a significant increase in heat sensations at the ear in both groups following exposure. However, this effect was observed only in one of the three techniques used for scoring heat sensations and the authors reported that the result may, therefore, have been a chance finding [Hillert et al., 2008]. In another study, significant differences between the IEI-EMF and control groups in the ability of participants to differentiate between conditions, was noted [Kim et al., 2008]. However, this effect mainly reflected the greater tendency of IEI-EMF participants to reply 'yes' when asked the prompt question 'do you feel EMF?' Despite this, the accuracy of IEI-EMF participants in detecting the genuine EMF exposure in this study was only 42.2%, less than the 50% rate that would be expected by chance alone.

Mobile Phone Base Station Experiments

The results for the mobile phone base station experiments are shown in Table 2. In one study, participants randomised to receive higher levels of exposure reported significantly higher levels of 'calmness' than those who received lower levels of exposure [Augner et al., 2009]. However, this effect was identified only when both the control and IEI-EMF groups were combined together and was no longer observed once the authors corrected for the number of endpoints tested [Augner et al., 2009]. In another study, exposure to UMTS (3G) signals was found to be significantly associated with higher levels of agitation

TABLE 1. Provocation Studies Using Mobile Phone Handset-Related Exposures

Refs	Sample	Active stimulus	Number of exposures	Total number of correct discriminations between active and sham (number of participants successfully discriminating)	Type of self-report symptoms measured and comparison between active and inactive conditions (results all $P > 0.05$ unless indicated)
Bamiou et al. [2008]	9 IEI-EMF, 21 controls	GSM handset exposure (882 MHz), and a carrier wave (CW) signal	Six 30 min exposures: two GSM, two CW, and two sham	For both groups combined: 77/180 (43%). There was no significant difference in mean number of correct guesses between IEI-EMF and controls (IEI-EMF: 0/9, Control: 0/21)	None
Hillert et al. [2008]	38 IEI-EMF, 33 controls	GSM handset exposure (884 MHz)	Two exposures: one GSM, one sham	IEI-EMF: 26/75 (35%) (2/37), control: 21/62 (34%) (5/31)	Headache (control group: more headache in the active condition, $P < 0.05$), fatigue, nausea, vertigo, difficulty concentrating, feeling low-spirited, vision problems, dermal complaints, stress, ear heat (higher scores for both groups in active condition ($P < 0.05$)), ear pain, other
Kim et al. [2008]	18 IEI-EMF, 19 controls	CDMA handset (835 MHz)	Two 30 min exposures: one CDMA and one sham	IEI-EMF: accuracy for exposure = 42%, accuracy for non-exposure = 74%. Control: accuracy for exposure = 3%, accuracy for non-exposure = 95%. Significant differences ($P < 0.01$) between groups for both exposure types	Redness, itching, throbbing, burning, fatigue, headache, dizziness, nausea, palpitation, indigestion
Kwon et al. [2008]	6 IEI-EMF, 78 controls	GSM handset exposure (902 MHz)	Minimum of 600 trials per participant of active or sham stimulus. Each condition lasted for 5 s	Mean correct response rate for IEI-EMF ($n = 6$, 100 'on/off' trials) = 47% and for most controls ($n = 76$, 100 'on/off' trials) = 51% (After retesting three participants: IEI-EMF 0/6, control 0/78)	None
Oftedal et al. [2007]	17 IEI-EMF	GSM handset exposure (902.4 MHz)	Up to eight 30 min trials per participant (four active and four sham for most participants)	IEI-EMF: 52/129 (40%)	Headache, 'any other symptoms' affecting the head
Rubin et al. [2006b]	69 IEI-EMF, 60 controls	GSM handset exposure (900 MHz) and a CW signal	Three 50 min exposures per participant: one GSM, one CW and one sham	IEI-EMF: 110/192 (57%), controls: 96/180 (53%)	Headaches; nausea; fatigue; dizziness; skin itching, tingling or stinging; warmth or burning on skin; eye pain or dryness; 'severe reaction'
Wilen et al. [2006]	20 IEI-EMF, 20 controls	GSM handset exposure (900 MHz)	Two 30 min exposures: one GSM and one sham	Not reported	Whether the participant reported any symptoms during or after the experiment

GSM, General System for Mobile Communication; IEI-EMF, Idiopathic Environmental Intolerance with attribution to Electromagnetic Fields.

TABLE 2. Provocation Studies Using Mobile Phone Base Station-Related Exposures

Refs	Sample	Active stimulus	Number of exposures	Total number of correct discriminations between active and sham (number of participants successfully discriminating)	Type of self-report symptoms measured and comparison between active and inactive conditions (results all $P > 0.05$ unless indicated)
Augner et al. [2009]	8 IEI-EMF, 49 controls	Predominantly GSM base station exposure (900 MHz), with three intensities: 'low', 'medium' or 'high'	Five 50 min exposures, separated by 5 min breaks	Not reported	Good mood, alertness and calmness. 'No exposure/hypersensitivity-interaction was detected'. With IEI-EMF and control participants combined, participants randomised into groups which received one 'high' and one 'medium' exposure (in different orders, $n = 22$ and 26) had significantly higher calmness than participants who received low levels of exposure ($n = 9$, $P = 0.04$, and $P = 0.03$)
Eltiti et al. [2007]	44 IEI-EMF, 114 controls	GSM (combined 900 and 1800) and UMTS base station exposure	Three 50 min exposures: one to GSM, one to UMTS and one to sham. Plus three 5 min exposures, one to each condition	IEI-EMF: 73/132 (55.2%, 5 min exposures) and 79/132 (59.8%, 50 min exposures). Controls: 176/342 (51.4%, 5 min exposures) and 171/342 (50.1%, 50 min exposures) (IEI-EMF: 2/44, Control 5/114)	Anxiety, tension, agitation (IEI-EMF: UMTS vs. sham $P < 0.0025$), relaxation, discomfort, tiredness, plus overall symptom severity and occurrence for a list of 57 symptoms
Furubayashi et al. [2009]	11 IEI-EMF, 43 controls	Continuous exposure to W-CDMA base station exposure (2.14 GHz), and intermittent exposure with EMF randomly turned on and off every 5 min	Four 30 min sessions, consisting of the two active exposures, a sham exposure, and a sham exposure with noise as a stressor	During the intermittent exposure condition: IEI-EMF: 34/66 (52%). Controls: 126/258 (49%)	Tension, depression, anger, vigour, fatigue, confusion, discomfort
Regel et al. [2006]	33 IEI-EMF, 84 controls	UMTS base station exposure of 10 V/m or 1 V/m	Three 45 min exposures, one each to strong, weak or sham exposure	Mean perceived field strength, rated on a 0–100 scale, showed no significant association with actual field strength. IEI-EMF: 17/31 (55%), controls 22/57 (47%)	Tenseness, apprehension, worry, anxiety, being skeptical, unease, anxiety, somatic symptoms, inadequacy, depression, hostility

GSM, General System for Mobile Communication; IEI-EMF, Idiopathic Environmental Intolerance with attribution to Electromagnetic Fields; UMTS, Universal Mobile Telecommunications System.

in the IEI-EMF group [Eltiti et al., 2007]. However, further analyses controlling for the order in which the active and sham exposures were presented suggested that this effect was an artefact 'most likely due to a higher proportion of sensitive individuals receiving the UMTS signal first' [Eltiti et al., 2007], although this interpretation has been the subject of some debate [Eltiti et al., 2008; Roosli and Huss, 2008]. The other two studies in this category reported no significant effect of exposure [Regel et al., 2006; Furubayashi et al., 2009].

Magnetic Field Experiments

Of the four studies using magnetic field exposures (Table 3) [Frick et al., 2005; Wenzel et al., 2005; David et al., 2006; Landgrebe et al., 2008b], two reported significant differences between IEI-EMF participants and control participants [Frick et al., 2005; Landgrebe et al., 2008b]. In both cases, however, these differences reflected a reduced ability of IEI-EMF participants to discriminate between genuine and sham stimulation, resulting from an increased tendency of IEI-EMF participants to report physical sensations during the sham exposures.

Other Experiments

In one final study (Table 4), 43 IEI-EMF participants spent three nights at home sleeping under protective netting designed to shield them from electromagnetic fields, three nights under sham netting and three nights under no netting [Leitgeb et al., 2008]. Three participants experienced significant benefits in terms of subjective sleep quality from the genuine netting, in comparison to the other two conditions. However, subsequent checks of monitoring equipment installed inside the netting revealed 'suspicious' changes in electromagnetic field levels during the evenings for each of these volunteers. The authors concluded that the participants may have been checking whether the netting was genuine or sham and advised that 'these faking volunteers could not be considered as evidence for anything, in particular not for causal effects of (radiofrequency field) immissions (sic) on sleep' [Leitgeb et al., 2008].

TABLE 3. Provocation Studies Using Magnetic Field Exposures

Ref	Sample	Active stimulus	Number of exposures	Total number of correct discriminations between active and sham (number of participants successfully discriminating)	Type of self-report symptoms measured and comparison between active and inactive conditions (results all $P > 0.05$ unless indicated)
Frick et al. [2005]	30 IEI-EMF, 27 controls: high symptoms, 28 controls: low symptoms	Transcranial magnetic pulses to the dorsolateral prefrontal cortex of increasing magnitude	Four series of 19 tests per participant. Two series involved increasing output capacity of the magnetic coil, with 3% increments, rising from 0% to 57% of 1.8 T. A sham coil with no output was applied for the other two series	No significant differences between the groups in detection thresholds for the genuine magnetic coil. IEI-EMF participants had 'significantly' worse ability to discriminate magnetic from sham coils compared to the high symptom load control group	None
Landgrebe et al. [2008b]	88 IEI-EMF, 107 controls	Transcranial magnetic pulses to the dorsolateral prefrontal cortex of increasing magnitude	Four series of 19 tests per participant. Two series with increasing magnetic coil output, with 3% increments, from 0% to 57% of 1.8 T. A sham coil with no output was applied for the other two series	No significant differences between the groups in detection thresholds for the genuine magnetic coil. IEI-EMF participants had worse ability to discriminate magnetic from sham coils compared to the control group ($P = 0.01$)	None
David et al. [2006]	'More than' 50 IEI-EMF, similar number of controls	50 Hz magnetic flux densities of 10 μT	Twenty 2 min exposures per participant: 10 of the active condition, 10 of a sham condition	'The rating of field situation by (IEI-EMF) during exposure in weak fields did not differ from healthy controls'	None
Wenzel et al. [2005]	3 IEI-EMF, 7 controls	Total body exposure to 50 Hz magnetic flux of 96 mT	Ten 5 min exposures, five of the active condition and five of a sham condition	Not reported	Any sensations experienced during the experiment

IEI-EMF, Idiopathic Environmental Intolerance with attribution to Electromagnetic Fields.

TABLE 4. Other Provocation Studies

Refs	Sample	Active stimulus	Number of exposures	Total number of correct discriminations between active and sham (number of participants successfully discriminating)	Type of self-report symptoms measured and comparison between active and inactive conditions (results all $P > 0.05$ unless indicated)
Leitgeb et al. [2008]	43 IEI-EMF	A Faraday cage of electric conductive material mounted around the participant's own bed at home	Nine nights of sleep: three were under the genuine protective material, three under sham material, and three under no material	Not assessed	Sleep quality, awakening quality, sleep efficiency, overall sleep score. Three participants showed results indicating significant ($P < 0.05$) improvements in total sleep score in the genuine protective condition compared to the other two conditions, as well as significant improvements in sleep quality ($n = 1$), awakening quality ($n = 1$) or sleep efficiency ($n = 1$). However, subsequent checks revealed that all three participants appeared to have unblinded the study

IEI-EMF, Idiopathic Environmental Intolerance with attribution to Electromagnetic Fields.

DISCUSSION

Current Evidence

In our original review of 31 provocation studies for IEI-EMF, we reported being 'unable to find any robust evidence to support the existence of (electromagnetic hypersensitivity) as a biologic entity' [Rubin et al., 2005]. Five years and 15 experiments later, this update has failed to uncover any evidence which challenges that conclusion. While seven studies did report some effects of exposure on IEI-EMF participants, without exception these effects had either methodological explanations, be it a type 1 error due to multiple testing [Hillert et al., 2008; Augner et al., 2009], an effect caused by the order of exposure [Eltiti et al., 2007] an unblinding of the study by the participants [Leitgeb et al., 2008], or they reflected an increased tendency of IEI-EMF participants to claim to have detected the presence of EMF, regardless of the accuracy of these claims [Frick et al., 2005; Kim et al., 2008; Landgrebe et al., 2008b]. At the same time, several studies included in this update contradicted two of the 'positive' studies identified in our original review [Mueller et al., 2000; Zwamborn et al., 2003]. In one of these, the original study reported a significant effect of mobile phone base station exposure on self-reported symptoms in IEI-EMF participants and in healthy control participants [Zwamborn et al., 2003]. Two studies included in this update consisted of explicit attempts to replicate these findings; neither was able to do so [Regel et al., 2006; Eltiti et al., 2007], although questions have been raised about the adequacy of the statistical analysis in one of these replication attempts [Roosli and Huss 2008; Eltiti et al., 2008]. In the other study, our original review showed that night-time exposure to higher levels of electromagnetic fields resulted in significantly higher levels of pleasure and arousal upon awakening [Mueller et al., 2000]. However, a subsequent study failed to identify any effect of altering field levels on subjective sleep parameters [Leitgeb et al., 2008]. The evidence that IEI-EMF symptoms are related to exposure to electromagnetic fields is, therefore, now weaker than it was at the time of our original review.

This conclusion is in agreement with most other reviews of this area [Seitz et al., 2005; Hillert et al., 2006; Roosli, 2008; SCENIHR, 2009], with one notable exception: the 'Bioinitiative Report' [Carpenter and Sage, 2007]. Subsection seven of section nine in this report dealt with 'human subjective effects' of exposure to mobile phone signals and stated that 'none of these effects has been studied under controlled laboratory conditions. Thus, whether they are causally related to (mobile phone) exposure is unknown'. Given that seven relevant studies were reported in our original review [Rubin et al., 2005], 12 further studies were identified in this update (Tables 1,2 and 4) and at least six additional provocation studies involving only healthy volunteers have also been reported [Roosli, 2008], we are unable to explain how this conclusion was reached.

While this update has provided no support for the theory that bioelectromagnetic mechanisms are responsible for IEI-EMF, additional support was found for the theory that psychological factors have an important role in triggering, maintaining or exacerbating IEI-EMF symptoms [Rubin et al., 2007]. In particular, although no specific effects of active exposure were found in the studies that we identified, many studies noted that both active and sham conditions were equally effective in triggering symptoms [Wenzel et al., 2005;

Wilen et al., 2006; Rubin et al., 2006b; Eltiti et al., 2007; Oftedal et al., 2007; Hillert et al., 2008; Leitgeb et al., 2008; Furubayashi et al., 2009]. Given that sham exposures appear sufficient to trigger the symptoms reported by IEI-EMF participants in the laboratory, it seems likely that similar 'nocebo' effects may also account for many of the acute symptoms that they experience in everyday life. This mechanism would predict that conscious expectation of symptoms following perceived exposure to electrical devices results in the formation or detection of symptoms, while heightened vigilance for possible indicators of exposure leads to a higher frequency of such effects occurring [Frick et al., 2005; Landgrebe et al., 2008b]. In support of this, one study not included in this review has demonstrated that triggering symptom expectations by deceiving IEI-EMF participants into thinking that they are being exposed to a mobile phone signal does indeed result in symptom formation, accompanied by activation of brain regions previously shown to be involved in pain perception [Landgrebe et al., 2008a].

Quality of the Current Evidence

Provocation studies for any variant of IEI can be difficult to conduct [Das Munshi et al., 2007]. From a pragmatic point of view, recruiting sufficient numbers of participants is often the hardest challenge, explaining why many of the studies we reviewed have been relatively small (median number of IEI-EMF participants = 19). However, while it is possible that reduced statistical power resulting from low sample sizes may have restricted the ability of individual studies to identify a genuine effect of exposure, the consistency in which this finding has been reported throughout the literature suggests that this is not the reason for the overall failure of provocation studies to support the bioelectromagnetic theory of IEI-EMF. This conclusion is also supported by results of a recent meta-analysis which pooled together outcomes from five mobile phone-related studies (combined $n = 180$), and still failed to identify any significant effect of exposure [Roosli, 2008]. Nonetheless, we would recommend that researchers, and their funding bodies, ensure that future studies are allowed sufficient time and money to recruit enough participants to meet the study objectives: additional small-scale or pilot studies are unlikely to substantially advance this literature.

As well as allowing more time for recruitment, two other ways to increase sample sizes are to advertise widely for participants (e.g., through newspaper articles, approaches to support groups or via referrals from clinicians) and to adopt broader inclusion criteria allowing sufferers with differing subjective experiences or levels of impairment to take part. Both of these approaches have been used in several of the studies included in this review [Rubin et al., 2006b] and both have been criticised for increasing the heterogeneity of a study's sample [Schrottner et al., 2007; Hillert et al., 2008]. Is it helpful, for example to include participants who describe numerous symptoms associated with multiple electrical and chemical stimuli along with participants whose sole concern is that they experience headaches when using their mobile phone? In practice, however, several recent studies have deliberately used homogenous samples of participants who reported sensitivity to mobile phones alone: these too have failed to identify any robust effect of exposure [e.g. Wilen et al., 2006; Oftedal et al., 2007; Hillert et al., 2008].

A slightly more complex homogeneity issue concerns whether only a small subset of those who report IEI-EMF, regardless of its severity, are actually sensitive to electromagnetic fields while the majority suffer from unrelated conditions and/or nocebo reactions. If true, this would adversely affect the ability of studies which rely on group means or overall response frequencies to test the bioelectromagnetic theory of IEI-EMF. It should be noted, however, that 21 studies used designs in which individual participants were repeatedly exposed to sham or active stimuli and reported data enabling the identification of individuals who were reliably able to discriminate one form of exposure from the other. These include three studies reported in this update that involved 6–600 exposures per participant [Eltiti et al., 2007; Bamiou et al., 2008; Kwon et al., 2008] and 18 studies reported in our original review [Rubin et al., 2005]. Of the 378 participants tested in this way, only 11 (2.9%) appeared able to make this distinction, with a similar proportion of healthy control participants also falling into this category (7 out of 292 (2.4%)). While differences between the studies in terms of the number of tests used and the statistical criteria employed for identifying someone as 'reliably able to discriminate' make it difficult to perform any meta-analysis, it seems likely that these figures are no higher than might be expected by chance. Of particular interest is one study in which participants were exposed to EMF or sham conditions up to several hundred times each [Kwon et al., 2008]. Although this study did identify two healthy control participants who achieved remarkable success in one round of 100 exposures, identifying over 90% of them correctly, neither participant was subsequently able to replicate their performance.

Aside from issues surrounding the recruitment of participants, a second set of concerns relates to the ecological validity of provocation studies. This issue encompasses uncertainty as to whether carefully

constructed chambers which screen out extraneous electromagnetic fields increase the chances of detecting an effect of exposure or removes important (if unknown) synergistic elements present in the environment; that attendance at a laboratory may cause anxiety for participants which may affect their results [Eltiti et al., 2007; Augner et al., 2009]; that exposure produced using specially designed equipment as opposed to, say, a genuine mobile phone, may miss some important element of exposure that is essential for triggering symptoms [Oftedal et al., 2007]; that low-level leakage from the equipment during sham exposures may invalidate any comparison [Rubin et al., 2006b]; that other environmental stimuli encountered in the laboratory or on a participant's journey to the laboratory may themselves trigger symptoms; and criticism that follow-up times in laboratory experiments are insufficiently long to capture a participant's response. Although none of these issues is entirely without foundation, the importance of them can be overstated. In particular, the use by several studies of non-blind 'practice' sessions involving the active exposure condition have explicitly demonstrated that the artificiality of a laboratory setting does not prevent participants from experiencing their usual IEI symptoms [Rubin et al., 2005; Eltiti et al., 2007; Oftedal et al., 2007]. At the same time, the high level of confidence reported by participants in their ability to detect which condition is which, in many of these studies, also suggests that the participants themselves believe these experiments to be a fair test of their sensitivities [Rubin et al., 2005, 2006b]. Meanwhile, several studies have deliberately used a more naturalistic setting without noting any robust effect of exposure [Rubin et al., 2005].

While the majority of people with IEI-EMF report that their symptoms usually occur within minutes to hours after exposure, a minority of sufferers report a lengthier onset, with an accumulation of exposure over days or weeks seen as causing increased symptom severity [Roosli et al., 2004]. While most provocation studies have used short-term exposures to test the former type of IEI-EMF, the more chronic form of the condition remains underinvestigated. To date, three double-blind experiments have used real or sham shielding material to test whether reducing electromagnetic fields in a participant's workplace or home for periods between 3 days and 3 months is effective in reducing symptoms: these studies have not produced any convincing evidence for such an effect [Oftedal et al., 1995, 1999; Leitgeb et al., 2008]. Although care must be taken to ensure that the double-blinding of such studies is not compromised by the understandable inquisitiveness of some participants [Leitgeb et al., 2008], additional research using this paradigm would be of interest.

CONCLUSIONS

To date, 46 studies involving 1175 volunteers with IEI-EMF have tested whether exposure to electromagnetic fields can trigger the symptoms reported by this group. These studies have produced little evidence to suggest that this is the case or that individuals with IEI-EMF are particularly adept at detecting the presence of electromagnetic fields. On the other hand, many of these studies have found evidence that the nocebo effect is a sufficient explanation for the acute symptoms reported in IEI-EMF. Thus while continued experimental research in this area will be required to clarify the role of chronic exposures and to test the effects of new varieties of electromagnetic emissions, the best evidence currently available suggests that IEI-EMF should not be viewed as a bioelectromagnetic phenomenon. Despite this, some commentators continue to discuss the condition without sufficient reference to this literature [Carpenter and Sage, 2007; Goldacre, 2007]. This is regrettable and suggests that the scientific community should do more to communicate the current state of the art in this area.

In the meantime, when faced with someone who describes subjective symptoms that are apparently associated with exposure to an electrical device, it would be wise for clinicians and policy makers to begin with the assumption that an alternative explanation for these symptoms may be present, either in the form of a conventional organic or psychiatric disorder, or in terms of the more subtle psychological processes associated with the nocebo response. In the latter case, treatment based on cognitive behaviour therapy may be helpful for some patients [Rubin et al., 2006a].

REFERENCES

Augner C, Florian M, Pauser G, Oberfeld G, Hacker GW. 2009. GSM base stations: Short-term effects on well-being. Bioelectromagnetics 30:73–80.

Bamiou DE, Ceranic B, Cox R, Watt H, Chadwick P, Luxon LM. 2008. Mobile telephone use effects on peripheral audiovestibular function: A case-control study. Bioelectromagnetics 29:108–117.

Barnett J, Timotijevic L, Vassallo M, Sheperd R. 2008. Precautionary advice about mobile phones: Public understandings and intended responses. J Risk Res 11:525–540.

Blettner M, Schlehofer B, Breckenkamp J, Kowall B, Schmeidel S, Reis U, Potthoff P, Schuez J, Berg-Beckhoff G. 2009. Mobile phone base stations and adverse health effects: Phase 1: A population-based cross-sectional study in Germany. Occup Environ Med 66:118–123.

Burgess A. 2004. Cellular phones, public fears, and a culture of precaution. Cambridge: Cambridge University Press.

Carlsson F, Karlson B, Orbaek P, Osterberg K, Ostergren P-O. 2005. Prevalence of annoyance attributed to electrical equipment and smells in a Swedish population, and relationship with subjective health and daily functioning. Public Health 119: 568–577.

Carpenter D, Sage C. 2007. Bioinitiative Report: A Rationale for a Biologically-Based Public Exposure Standard for Electromagnetic Fields (ELF and RF). Available from www.bioinitiative.org.

Das Munshi J, Rubin GJ, Wessely S. 2007. Multiple chemical sensitivities: A systematic review of provocation studies. J Allergy Clin Immunol 118:1257–1264.

David E, Reissenweber J, Wojtysiak A. 2006. Provocation studies in electromagnetically hypersensitive persons. In Hansson Mild K, Repacholi M, van Deventer E, Ravazzani P (editors). Electromagnetic Hypersensitivity. Proceedings: International Workshop on EMF Hypersensitivity. Prague: WHO. pp. 123–133.

Eltiti S, Wallace D, Ridgewell A, Zougkou K, Russo R, Sepulveda F, Mirshekar-Syahkal D, Rasor P, Deeble R, Fox E. 2007. Does short-term exposure to mobile phone base station signals increase symptoms in individuals who report sensitivity to electromagnetic fields? A double-blind randomized provocation study. Environ Health Perspect 115:1603–1608.

Eltiti S, Wallace D, Ridgewell A, Russo R, Fox E. 2008. Mobile phone basestations: Eltiti et al. respond. Environ Health Perspect 116:A64–A65.

Frick U, Kharraz A, Hauser S, Wiegand R, Rehm J, Von Kovatsits U, Eichhammer P. 2005. Comparison perception of singular transcranial magnetic stimuli by subjectively electrosensitive subjects and general population controls. Bioelectromagnetics 26:287–298.

Furubayashi T, Ushiyama A, Terao Y, Mizuno Y, Shirasawa K, Pongpaibool P, Simba AY, Wake K, Nishikawa M, Miyawaki K, Yasuda A, Uchiyama M, Yamashita HK, Masuda H, Hirota S, Takahashi M, Okano T, Inomata-Terada S, Sokejima S, Maruyama E, Watanabe S, Taki M, Ohkubo C, Ugawa Y. 2009. Effects of short-term W-CDMA mobile phone base station exposure on women with or without mobile phone related symptoms. Bioelectromagnetics 30: 100–113.

Goldacre B. 2007. Why don't journalists mention the data? Br Med J 334:1249.

Hillert L, Berglind N, Arnetz BB, Bellander T. 2002. Prevalence of self-reported hypersensitivity to electric or magnetic fields in a population-based questionnaire survey. Scand J Work Environ Health 28:33–41.

Hillert L, Leitgeb N, Meara J. 2006. Working group report. In Hansson Mild K, Repacholi M, van Deventer E, Ravazzani P (editors). Electromagnetic Hypersensitivity. Proceedings: International Workshop on EMF Hypersensitivity. Prague: WHO. pp. 15–26.

Hillert L, Åkerstedt T, Lowden A, Wiholm C, Kuster N, Ebert S, Boutry C, Moffat SD, Berg M, Arnetz BB. 2008. The effects of 884 MHz GSM wireless communication signals on headache and other symptoms: An experimental provocation study. Bioelectromagnetics 29:185–196.

Kim DW, Lee JH, Ji HC, Kim SC, Nam KC, Cha EJ. 2008. Physiological effects of RF exposure on hypersensitive people by a cell phone. 30th Annual International IEEE EMBS Conference. 2322–5.

Kwon MS, Koivisto M, Laine M, Hamalainen H. 2008. Perception of the electromagnetic field emitted by a mobile phone. Bioelectromagnetics 29:154–159.

Landgrebe M, Barta W, Rosengarth K, Frick U, Hauser S, Langguth B, Rutschmann R, Greenlee MW, Hajak G, Eichhammer P. 2008a. Neuronal correlates of symptom formation in functional somatic syndromes: A fMRI study. NeuroImage 41: 1336–1344.

Landgrebe M, Frick U, Hauser S, Langguth B, Rosner R, Hajak G, Eichhammer P. 2008b. Cognitive and neurobiological alterations in electromagnetic hypersensitive patients: Results of a case-control study. Psychol Med 38:1781–1791.

Leitgeb N, Schröttner J, Cech R, Kerbl R. 2008. EMF-protection sleep study near mobile phone base stations. Somnologie 12:234–243.

Levallois P, Neutra R, Lee G, Hristova L. 2002. Study of self-reported hypersensitivity to electromagnetic fields in California. Environ Health Perspect 110(Suppl 4):619–623.

Mortazavi SMJ, Ahmadi J, Shariati M. 2007. Prevalence of subjective poor health symptoms associated with exposure to electromagnetic fields among university students. Bioelectromagnetics 28:326–330.

Mueller CH, Krueger H, Schierz C. 2000. Project NEMESIS: Double-blind study on effects of 50Hz EMF on sleep quality and physiological parameters in people suffering from electrical hypersensitivity. The Bioelectromagnetics Society 22nd Annual Meeting, Munich, Germany. 89–90.

Oftedal G, Vistnes AI, Rygge K. 1995. Skin symptoms after the reduction of electric-fields from visual-display units. Scand J Work Environ Health 21:335–344.

Oftedal G, Nyvang A, Moen BE. 1999. Long-term effects on symptoms by reducing electric fields from visual display units. Scand J Work Environ Health 25:415–421.

Oftedal G, Straume A, Johnsson A, Stovner LJ. 2007. Mobile phone headache: A double-blind, sham-controlled provocation study. Cephalalgia 27:447–455.

Regel SJ, Negovetic S, Roosli M, Berdinas V, Schuderer J, Huss A, Lott U, Kuster N, Achermann P. 2006. UMTS base station-like exposure, well-being, and cognitive performance. Environ Health Perspect 114:1270–1275.

Reissenweber J, David E, Kentner S. 2000. Different aspects of electromagnetic hypersensitivity. The Bioelectromagnetics Society 22nd Annual Meeting, Munich, Germany. 270–271.

Roosli M. 2008. Radiofrequency electromagnetic field exposure and non-specific symptoms of ill health: A systematic review. Environ Res 107:277–287.

Roosli M, Huss A. 2008. Mobile phone base station exposure and symptoms. Environ Health Perspect 116:A62–A63.

Roosli M, Moser M, Baldinini Y, Meier M, Braun-Fahrlander C. 2004. Symptoms of ill health ascribed to electromagnetic field exposure—A questionnaire survey. Int J Hygiene Environ Health 207:141–150.

Rubin GJ, Das Munshi J, Wessely S. 2005. Electromagnetic hypersensitivity: A systematic review of provocation studies. Psychosom Med 67:224–232.

Rubin GJ, Das Munshi J, Wessely S. 2006a. A systematic review of treatments for electromagnetic hypersensitivity. Psychother Psychosom 75:12–18.

Rubin GJ, Hahn G, Everitt B, Cleare AJ, Wessely S. 2006b. Are some people sensitive to mobile phone signals? A within-participants, double-blind, randomised provocation study. Br Med J 332:886–889.

Rubin GJ, Cleare AJ, Wessely S. 2007. Psychological factors associated with self-reported sensitivity to mobile phones. J Psychosom Res 64:1–9.

Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR). 2009. Health effects of exposure to EMF. Brussels: European Commission.

Schrottner J, Leitgeb N, Hillert L. 2007. Investigation of electric current perception thresholds of different EHS groups. Bioelectromagnetics 28:208–213.

Seitz H, Stinner D, Eikmann Th, Herr C, Roosli M. 2005. Electromagnetic hypersensitivity (EHS) and subjective health complaints associated with electromagnetic fields of mobile phone communication—A literature review published between 2000 and 2004. Sci Total Environ 349: 45–55.

Stewart W. 2008. The Stewart Report—Then, now and the foreseeable future. Health Protection Matters 12:4–6.

Wenzel F, Reissenweber J, David E. 2005. Cutaneous microcirculation is not altered by a weak 50 Hz magnetic field. Biomed Tech (Berl) 50:14–18.

Wilen J, Johansson A, Kalezic N, Lyskov E, Sandstrom M. 2006. Psychophysiological tests and provocation of subjects with mobile phone related symptoms. Bioelectromagnetics 27: 204–214.

Zwamborn APM, Vossen SHJA, van Leersum BJAM, Ouwens MA, Makel WN. 2003. Effects of Global Communication System radio-frequency fields of well being and cognitive functions of human subjects with and without subjective symptoms. The Hague: Netherlands Organisation for Applied Scientific Research (TNO).

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Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

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Abstract

Objectives To determine whether parachutes are effective in preventing major trauma related to gravitational challenge.
Design Systematic review of randomised controlled trials.
Data sources: Medline, Web of Science, Embase, and the Cochrane Library databases; appropriate internet sites and citation lists.
Study selection: Studies showing the effects of using a parachute during free fall.
Main outcome measure Death or major trauma, defined as an injury severity score > 15.
Results We were unable to identify any randomised controlled trials of parachute intervention.
Conclusions As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.

Introduction

The parachute is used in recreational, voluntary sector, and military settings to reduce the risk of orthopaedic, head, and soft tissue injury after gravitational challenge, typically in the context of jumping from an aircraft. The perception that parachutes are a successful intervention is based largely on anecdotal evidence. Observational data have shown that their use is associated with morbidity and mortality, due to both failure of the intervention[1 2] and iatrogenic complications.[3] In addition, "natural history" studies of free fall indicate that failure to take or deploy a parachute does not inevitably result in an adverse outcome.[4] We therefore undertook a systematic review of randomised controlled trials of parachutes.

Methods

Literature search

We conducted the review in accordance with the QUOROM (quality of reporting of meta-analyses) guidelines.[5] We searched for randomised controlled trials of parachute use on Medline, Web of Science, Embase, the Cochrane Library, appropriate internet sites, and citation lists. Search words employed were "parachute" and "trial." We imposed no language restriction and included any studies that entailed jumping from a height greater than 100 metres. The accepted intervention was a fabric device, secured by strings to a harness worn by the participant and released (either automatically or manually) during free fall with the purpose of limiting the rate of descent. We excluded studies that had no control group.

Definition of outcomes

The major outcomes studied were death or major trauma, defined as an injury severity score greater than 15.[6]

Meta-analysis

Our statistical apprach was to assess outcomes in parachute and control groups by odds ratios and quantified the precision of estimates by 95% confidence intervals. We chose the Mantel-Haenszel test to assess heterogeneity, and sensitivity and subgroup analyses and fixed effects weighted regression techniques to explore causes of heterogeneity. We selected a funnel plot to assess publication bias visually and Egger's and Begg's tests to test it quantitatively. Stata software, version 7.0, was the tool for all statistical analyses.

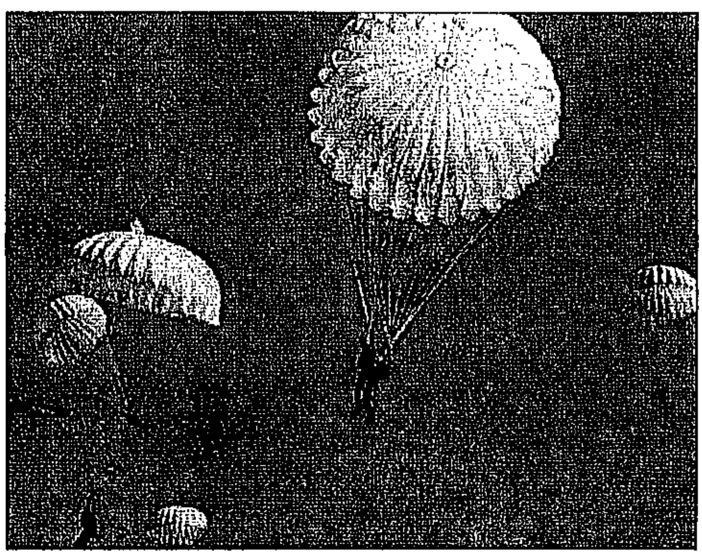
Results

Our search strategy did not find any randomised controlled trials of the parachute.

Discussion

Evidence based pride and observational prejudice

It is a truth universally acknowledged that a medical intervention justified by observational data must be in want of verification through a randomised controlled



Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

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trial. Observational studies have been tainted by accusations of data dredging, confounding, and bias.[7] For example, observational studies showed lower rates of ischaemic heart disease among women using hormone replacement therapy, and these data were interpreted as advocating hormone replacement for healthy women, women with established ischaemic heart disease, and women with risk factors for ischaemic heart disease.[8] However, randomised controlled trials showed that hormone replacement therapy actually increased the risk of ischaemic heart disease,[9] indicating that the apparent protective effects seen in observational studies were due to bias. Cases such as this one show that medical interventions based solely on observational data should be carefully scrutinised, and the parachute is no exception.

Natural history of gravitational challenge

The effectiveness of an intervention has to be judged relative to non-intervention. Understanding the natural history of free fall is therefore imperative. If failure to use a parachute were associated with 100% mortality then any survival associated with its use might be considered evidence of effectiveness. However, an adverse outcome after free fall is by no means inevitable. Survival has been reported after gravitation challenges of more than 10 000 metres (33 000 feet).[4] In addition, the use of parachutes is itself associated with morbidity and mortality.[1-3 10] This is in part due to failure of the intervention. However, as with all interventions, parachutes are also associated with iatrogenic complications.[3] Therefore, studies are required to calculate the balance of risks and benefits of parachute use.

The parachute and the healthy cohort effect

One of the major weaknesses of observational data is the possibility of bias, including selection bias and reporting bias, which can be obviated largely by using randomised controlled trials. The relevance to parachute use is that individuals jumping from aircraft without the help of a parachute are likely to have a high prevalence of pre-existing psychiatric morbidity. Individuals who use parachutes are likely to have less psychiatric morbidity and may also differ in key demographic factors, such as income and cigarette use. It follows, therefore, that the apparent protective effect of parachutes may be merely an example of the "healthy cohort" effect. Observational studies typically use multivariate analytical approaches, using maximum likelihood based modelling methods to try to adjust estimates of relative risk for these biases. Distasteful as these statistical adjustments are for the cognoscenti of evidence based medicine, no such analyses exist for assessing the presumed effects of the parachute.

The medicalisation of free fall

It is often said that doctors are interfering monsters obsessed with disease and power, who will not be satisfied until they control every aspect of our lives (*Journal of Social Science*, pick a volume). It might be argued that the pressure exerted on individuals to use parachutes is yet another example of a natural, life enhancing experience being turned into a situation of fear and dependency. The widespread use of the parachute may just be another example of doctors' obsession with disease prevention and their misplaced belief in unproved technology to provide effective protection against occasional adverse events.

What is already known about this topic

Parachutes are widely used to prevent death and major injury after gravitational challenge

Parachute use is associated with adverse effects due to failure of the intervention and iatrogenic injury

Studies of free fall do not show 100% mortality

What this study adds

No randomised controlled trials of parachute use have been undertaken

The basis for parachute use is purely observational, and its apparent efficacy could potentially be explained by a "healthy cohort" effect

Individuals who insist that all interventions need to be validated by a randomised controlled trial need to come down to earth with a bump

Parachutes and the military industrial complex

However sinister doctors may be, there are powers at large that are even more evil. The parachute industry has earned billions of dollars for vast multinational corporations whose profits depend on belief in the efficacy of their product. One would hardly expect these vast commercial concerns to have the bravery to test their product in the setting of a randomised controlled trial. Moreover, industry sponsored trials are more likely to conclude in favour of their commercial product,[11] and it is unclear whether the results of such industry sponsored trials are reliable.

A call to (broken) arms

Only two options exist. The first is that we accept that, under exceptional circumstances, common sense might be applied when considering the potential risks and benefits of interventions. The second is that we continue our quest for the holy grail of exclusively evidence based interventions and preclude parachute use outside the context of a properly conducted trial. The dependency we have created in our population may make recruitment of the unenlightened masses to such a trial difficult. If so, we feel assured that those who advocate evidence based medicine and criticise use of interventions that lack an evidence base will not hesitate to demonstrate their commitment by volunteering for a double blind, randomised, placebo controlled, crossover trial.

Contributors: GCSS had the original idea. JPP tried to talk him out of it. JPP did the first literature search but GCSS lost it. GCSS drafted the manuscript but JPP deleted all the best jokes. GCSS is the guarantor, and JPP says it serves him right.

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1 Belmont PJ Jr, Taylor KF, Mason KT, Shawen SB, Polly DW Jr, Klemme WR. Incidence, epidemiology, and occupational outcomes of thoracolumbar fractures among US Army aviators. *J Trauma* 2001;50:855-61.

2 Bricknell MC, Craig SC. Military parachuting injuries: a literature review. *Occup Med (Lond)* 1999;49:17-26.

3 Laszkowski C, Hasenfuss S, Verhoff M, Weiler G. An unusual airplane crash—deadly life saver. Unintentional activation of an automated reserve opening device causing airplane accident. *Forensic Sci Int* 2002;125:250-3.
4 Highest fall survived without a parachute. In: Cunningham A. *Guinness world records 2002*. London: Guinness World Records, 2002.
5 Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF, for the QUOROM Group. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. *Lancet* 1999;354:1896-1900.
6 Lossius HM, Langhelle A, Reide F, Pillgram-Larsen J, Lossius TA, Laake P, et al. Reporting data following major trauma and analysing factors associated with outcome using the new Utstein style recommendations. *Resuscitation* 2001;50:263-72.
7 Davey Smith G, Ebrahim S. Data dredging, bias, or confounding. *BMJ* 2002;325:1437-8.
8 Pines A, Mijatovic V, van der Mooren MJ, Kenemans P. Hormone replacement therapy and cardioprotection: basic concepts and clinical considerations. *Eur J Obstet Gynecol Reprod Biol* 1997;71:193-7.
9 Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-33.
10 Lee CT, Williams P, Hadden WA. Parachuting for charity: is it worth the money? A 5-year audit of parachute injuries in Tayside and the cost to the NHS. *Injury* 1999;30:283-7.
11 Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ* 2003;326:1167-70.

Medicine in Egypt at the time of Napoleon Bonaparte

Thomas G Russell, Terence M Russell

The scientists and doctors who accompanied Napoleon to Egypt in 1798 undertook a survey that is one of the great intellectual achievements of the 19th century. It left a record of the health and wellbeing of the people, especialy in Cairo

In 1798 Napoleon Bonaparte conquered Egypt with an army of 55 000 men. With his army was a party of 300 men of science and letters whose objective was to record the culture of Egypt. The result was an extensive series of writings and engravings known as the *Description de L'Égypte*.[1] Part of this great work was devoted to recording the health and wellbeing of the people of Egypt, as observed by Bonaparte's surgeons and physicians. In this article we draw attention to some of their achievements.[2]

French men of medical science

The scientists were selected by Claude Louis Berthollet, who studied medicine and served on scientific committees during the French Revolution (fig 1). He placed in charge of the army's medical core Dr René-Nicolas Desgenettes, who was the expedition's chief medical officer. In Egypt, Desgenettes busied himself with the welfare of the French army and the wellbeing of the Egyptian people. He also read papers to the French Institute at Cairo on the causes of ophthalmia and infant mortality. Remarkably, he inoculated himself with pus from a suppurating bubo to fortify himself against bubonic plague. Desgenettes outlined ideas for a new hospital, a pharmacy, and a school of medicine at Cairo.

The celebrated French naturalist and anatomist Georges Léopold Cuvier was invited to participate. He declined because he was about to start his series of studies of comparative anatomy, published in 1800 as *Leçons d'anatomie comparée*. In his place went one of the most revered men of French medical science, Dr Dominique-Jean Larrey. Bonaparte called him "the most virtuous man I have ever known." One of Larrey's contributions to military medicine was the *ambulance volante* (flying ambulance) that enabled wounded men to be transported from the scene of conflict (fig 2). Larrey published his Egyptian medical researches as *Mémoires et Observations sur plusieurs Maladies*. He was later appointed doctor in surgery and medicine at Paris and was subsequently elevated to a peerage with the titles Monsieur Le Baron and Chevalier de la Légion d'Honneur.

Tribulations of the military

The French army had to march through the desert to Cairo. The soldiers were maddened by thirst, and their torment was increased by the image of a lake—their first experience of the illusion of a mirage. On reaching the Nile, the troops gorged themselves on watermelons, which carried their own hazards; scores of men became afflicted by waterborne bacteria and

Fig 1 Claude Louis Berthollet, the distinguished surgeon and chemist who was responsible for recruiting the men of science who accompanied Napoleon Bonaparte on his Egyptian campaign. The decoration in his lapel is that of a Grand Officer of the Order of the Legion d'Honneur

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The history of the discovery of the cigarette—lung cancer link: evidentiary traditions, corporate denial, global toll

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ABSTRACT

Lung cancer was once a very rare disease, so rare that doctors took special notice when confronted with a case, thinking it a once-in-a-lifetime oddity. Mechanisation and mass marketing towards the end of the 19th century popularised the cigarette habit, however, causing a global lung cancer epidemic. Cigarettes were recognised as the cause of the epidemic in the 1940s and 1950s, with the confluence of studies from epidemiology, animal experiments, cellular pathology and chemical analytics. Cigarette manufacturers disputed this evidence, as part of an orchestrated conspiracy to salvage cigarette sales. Propagandising the public proved successful, judging from secret tobacco industry measurements of the impact of denialist propaganda. As late as 1960 only one-third of all US doctors believed that the case against cigarettes had been established. The cigarette is the deadliest artefact in the history of human civilisation. Cigarettes cause about 1 lung cancer death per 3 or 4 million smoked, which explains why the scale of the epidemic is so large today. Cigarettes cause about 1.5 million deaths from lung cancer per year, a number that will rise to nearly 2 million per year by the 2020s or 2030s, even if consumption rates decline in the interim. Part of the ease of cigarette manufacturing stems from the ubiquity of high-speed cigarette making machines, which crank out 20 000 cigarettes per min. Cigarette makers make about a penny in profit for every cigarette sold, which means that the value of a life to a cigarette maker is about US$10 000.

Lung cancer has become a formidable disease, killing about 1.5 million people per year globally, extrapolating from a 2008 International Agency for Research on Cancer (IARC) risk assessment.[1] The tragedy is magnified by the fact that the overwhelming majority of these deaths, around 95%, are entirely preventable. Lung cancer today is primarily caused by the inhalation of smoke from cigarettes, which is also why the disease was quite rare prior to the 20th century. Lung cancer was not even recognised medically until the 18th century, and as recently as 1900 only about 140 cases were known in the published medical literature. The malady must have been occasionally misdiagnosed as tuberculosis (phthisis) or pneumonia or some other lung malaise, but we also know from detailed autopsy records in Germany that the disease cannot have been very common. Findings of primary lung tumours in the autopsied bodies of German research clinics rose dramatically in the second half of the 19th century, and even more dramatically in the first decade of the 20th. Isaac Adler summarised this evidence in 1912, in the world's first monograph on lung cancer, noting that the incidence of malignant neoplasms of the lung seemed to show 'a decided increase'. Adler mentioned the 'abuse of tobacco and alcohol' as one possible cause, while also commenting that the subject was 'not yet ready for final judgment'.[2]

Tobacco was apparently not even suspected as a cause of lung tumours until the final decade of the 19th century. In 1898, a medical student by the name of Hermann Rottmann in Würzburg proposed that tobacco dust—not smoke—might be causing the elevated incidence of lung tumours among German tobacco workers. Rottmann's mistake was not corrected until 1912, when Adler proposed that smoking might be to blame for the growing incidence of pulmonary tumours. Lung cancer was still a very rare disease; so rare, in fact, that medical professors when confronted with a case sometimes told their students they might never see another.[3] By the 1920s, however, surgeons were encountering the malady with increasing frequency, and started puzzling over what might be responsible. Smoking was commonly blamed, along with asphalt dust from newly tarred roads, industrial air pollution and latent effects from exposure to poison gas in the First World War or the global influenza pandemic of 1918–1919. These and a number of other theories were put forward as possible explanations for the rise of lung cancer, until evidence from multiple sources of enquiry made it clear that tobacco was by far and away the leading culprit.

CONVERGING LINES OF EVIDENCE

In the middle decades of the 20th century, four distinct lines of evidence converged to establish cigarette smoking as the leading cause of lung cancer. These are outlined below.

Population studies

These were among the first and most convincing forms of evidence. Scholars started noting the parallel rise in cigarette consumption and lung cancer, and by the 1930s had begun to investigate this relationship using the methods of case-control epidemiology. Franz Hermann Müller at Cologne Hospital in 1939 published the first such study, comparing 86 lung cancer 'cases' and a similar number of cancer-free controls.[4] Müller was able to show that people with lung cancer were far more likely than non-cancer controls to have smoked, a fact confirmed by Eberhard Schairer and Eric Schöniger at the University of Jena in an even more

ambitious study from 1943.[5] These German results were subsequently verified and amplified by UK and American scholars: in 1950 alone, five separate epidemiological studies were published, including papers by Ernst Wynder and Evarts Graham in the USA and Richard Doll and A Bradford Hill in England. All confirmed this growing suspicion, that smokers of cigarettes were far more likely to contract lung cancer than non-smokers. Further confirmation came shortly thereafter from a series of prospective 'cohort' studies, conducted to eliminate the possibility of recall bias. The theory here was that by following two separate and initially healthy groups over time, one smoking and one non-smoking, matched by age, sex, occupation and other relevant traits, you could find out whether smoking was a factor in the genesis of lung disease. The results were unequivocal: Doll and Hill in 1954 concluded that smokers of 35 or more cigarettes per day increased their odds of dying from lung cancer by a factor of 40.[6] Hammond and Horn, working with the American Cancer Society on another large cohort study, concluded that same year that the link had been proven 'beyond a reasonable doubt'.[7 8]

Animal experimentation

This was a second key line of evidence. 'Tobacco juice' had been shown to cause cancer on laboratory animals since the first decade of the century,[9] and a number of scholars had confirmed these results. The most active in this realm was the intrepid Angel H Roffo, founding director of Argentina's Institute of Experimental Medicine for the Study and Treatment of Cancer, who in 1931 showed that smoke condensed from the destructive distillation of tobacco could cause tumours when smeared on the hairless skins of rabbits.[10] Roffo in the 1930s and early 1940s published dozens of articles (mainly in German and Spanish) implicating smoking in the genesis of cancer, prompting enthusiastic endorsement from the German public health establishment but also ridicule from the cigarette industry. German tobacco manufacturers even established an entire journal—*Chronica Nicotiana*—and a scientific 'academy', the *Academia Nicotiana Internationalis*, to buttress the fortunes of tobacco, then under siege from public health activists.[11]

In 1953, a great deal of attention was given to an experiment by Ernst Wynder, Evarts Graham and Adele Croninger, showing that tumours could be generated by painting cigarette smoke tars onto the shaved backs of mice.[12] *Life* magazine devoted several pages to the story, and *Time* cited Graham's conclusion that the case against tobacco had now been proved 'beyond any doubt'.[13] Public confidence in tobacco was shaken, and stock prices of American cigarette manufacturers plummeted. Tobacco manufacturers saw this new 'health scare' as a mortal threat to their livelihood, and decided to organise a response. On December 14, 1953, at the Plaza Hotel in Manhattan, CEOs of the six largest tobacco manufacturers in the USA (all but Liggett) met to plan a response. The outcome was a far-reaching plan to refute the accumulating evidence, using adverts, 'white papers', press releases and corporate schmoozing with popular science writers and journalists. Support for (industry-friendly) science was a vital part of this enterprise: cigarette manufacturers called for 'more research' to resolve a purported 'controversy', and set out to reassure the public that the companies were taking charge. That campaign was by and large a success, judging from the fact that per capita consumption rebounded from its dip in 1953. Cigarette consumption in the USA would in fact continue to grow throughout the 1960s and 1970s, peaking at about 630 billion sticks in 1982 before starting to decline.

Cellular pathology

A third line of evidence for the cigarette–cancer link came from cellular pathology. Pathologists in the 1930s had started noticing the capacity of cigarette smoke to cause ciliastasis—the deadening of the tiny whip or hair-like structures lining the upper airway passages, structures known to be responsible for wafting particulate contaminants out of the lungs.[14] Suspicions started to grow that ciliastasis could cause cigarette smoke to become trapped in the lungs, causing cancer. Pathologists also started exploring whether damage from smoking could be discerned at the level of the cell. Anderson C Hilding in 1956 confirmed that smokers were experiencing pulmonary ciliastasis, but also that cilia were being deadened at precisely those parts of the lung where cancers were most likely to develop.[15] Oscar Auerbach about this same time showed (from autopsy studies) that precancerous changes could be detected in the cells of smokers—even in those who had died from other causes.[16]

Cancer-causing chemicals in cigarette smoke

A fourth line of evidence stemmed from the discovery of cancer-causing chemicals in cigarette smoke. Polycyclic aromatic hydrocarbons had been identified as carcinogenic constituents of coal tar in the 1930s, and the question then arose: might there not be similar compounds in cigarette smoke? Angel Roffo in Argentina was the first to identify polycyclic aromatic hydrocarbons in cigarette smoke from their distinctive spectrographic signatures, and for a time at least his was the most authoritative voice in this realm.[17] Roffo's work was taken seriously even by consultants working for the industry. In 1947, in an internal report to the Lorillard company, makers of Old Gold cigarettes, John B Fishel of Ohio State University acknowledged the presence of 'carcinogenic benzopyrene in tobacco tars', citing Roffo as an authority.[18] Tobacco industry laboratories conducted their own investigations: Brown and Williamson researchers identified benzpyrene in cigarette smoke in 1952, and by the end of the decade cigarette manufacturers had characterised several dozen carcinogens in cigarette smoke, including arsenic, chromium, nickel and a veritable zoo of polycyclic aromatic hydrocarbons (chrysene, methylcholanthrene, dibenzanthracene, dibenzacridene, etc). As Philip Morris research director Helmut Wakeham put it in 1961, carcinogens were found in 'practically every class of compounds in cigarette smoke'.[19 20]

The confluence of these diverse forms of evidence—from epidemiology, animal experiments, clinical observation and chemical analysis, combined with diminishing evidence for alternative explanations, prompted health and medical authorities throughout the world to publicly acknowledge a cigarette–cancer link. The American Cancer Society's National Board of Directors in 1954 announced 'without dissent' that 'the presently available evidence indicates an association between smoking, particularly cigarette smoking, and lung cancer'. The Public Health Cancer Association that same year advised stopping smoking as a way to prevent cancer, and cancer authorities in Norway, Sweden, Finland, Denmark and The Netherlands came to similar conclusions. UK cancer authorities came on board, as did the Joint Tuberculosis Society of Great Britain and Canada's National Department of Health and Welfare.[21] Sceptics were converted, and medical attention shifted from the question of 'whether' to the question of 'how'—and what to do about it.

Researchers in the tobacco industry also became convinced of a cigarette–cancer link—though this was never admitted publicly. Claude Teague in his confidential 1953 'Survey of Cancer Research', written for upper management at RJ

Reynolds, makers of Camel cigarettes, concluded that the parallel rise in cigarette use and cancer had led to the suspicion that tobacco was 'an important etiologic factor in the induction of primary cancer of the lung'. Teague observed that clinical data were confirming the relationship, and concluded that the large body of animal experimental work 'would seem to indicate the presence of carcinogens'.[22]

Teague was not the only tobacco insider conceding a hazard. Harris Parmele, Lorillard's director of research, in 1946 had commented privately on how 'Certain scientists and medical authorities have claimed for many years that the use of tobacco contributes to cancer development in susceptible people. Just enough evidence has been presented to justify the possibility of such a presumption'.[23] The American Tobacco Company in the summer of 1953 took the extraordinary step of sponsoring a series of secret animal tests in the laboratories of the Ecusta Paper Corporation, makers of much of the world's cigarette paper, with the goal of finding out whether it was the tobacco leaf or the cigarette paper that was causing all this cancer. Their conclusion, distributed only privately, was that tobacco—and not the paper—was the culprit.[21]

Tobacco industry insiders by the mid 1950s clearly knew their product was dangerous. In December of 1953, when Hill and Knowlton was exploring how to respond to the uproar surrounding the publication of carcinogens in cigarette smoke, one tobacco company research director commented in a confidential interview: 'Boy! Wouldn't it be wonderful if *our* company was first to produce a cancer-free cigarette. What we could do to competition!' Another remarked on how fortunate it was 'for us' (ie, for cigarette manufacturers) that smokers were engaging in 'a habit they can't break'.[24] The mid-1950s cancer consensus was clearly (albeit privately) shared by the companies; and the reality of addiction was also starting to be conceded—at least in internal industry documents.

UK cigarette makers also commented on the lung cancer consensus. Three leading scientists from British American Tobacco (BAT) visited the USA in 1958, for example, and found that with only one exception all of those consulted—including dozens of experts inside and outside the industry—believed that a cancer connection had been proved.[25] Alan Rodgman at Reynolds 4 years later confessed that while evidence in favour of the cancer link was 'overwhelming', the evidence against was 'scant'.[26] Helmut Wakeham at Philip Morris about this same time drew up a list of dozens of carcinogens in cigarette smoke.[20] None of this was made public; indeed the tobacco industry throughout this time and for decades thereafter—until the end of the millennium—refused to admit any evidence of harms from smoking. No one can say precisely how many lives were lost as a result, but if the decline in per capita consumption that began with the US Surgeon General's report in 1964 had begun instead in 1954, when the conspiracy to challenge the science was launched, millions of lives would have been saved.[27]

The 1964 Surgeon General's report, which recognised smoking as a cause of lung cancer in men, is often regarded as a turning point in the recognition of health harms from smoking. But the Surgeon General's report was actually a kind of scientific anticlimax: from an evidentiary point of view the case against smoking had been closed by the end of the 1950s, and it was only the truculence and obstinacy of cigarette manufacturers that forced a blue-ribbon review by the federal government. Charles S Cameron, Medical and Scientific Director of the American Cancer Society, put the matter nicely in a 1956 overview for the *Atlantic Monthly*, noting that if the same level of evidence had been arrayed against, say, spinach, no one would have objected to the banning of that plant from the national diet.[28]

POPULAR KNOWLEDGE—AND IGNORANCE

History is, among other things, the study of origins and outcomes—how things come to be and disappear. The presumption is often of a certain contingency: how things turn out is often the outcome of struggles among competing agents. We've reviewed here the rise of scholarly knowledge of cigarette carcinogenicity, but it is also important to realise that popular knowledge, too, has a history. Scholars don't pay enough attention to what non-scholars think about the world, the proper study of which is agnotology.[29] What is the history of popular knowledge of the tobacco lung cancer link? What efforts have been made to generate ignorance?

One source of information for the history of ignorance is the polling data amassed by professional opinion research agencies and their tobacco industry counterparts. In 1954, for example, George Gallup sampled a broad swath of the US public to ask: 'do you think cigarette smoking is one of the causes of lung cancer, or not?' 41% answered 'yes', with the remainder answering either 'no' or 'undecided'.[30] Even large numbers of doctors remained unconvinced. In 1960, in a poll organised by the American Cancer Society, only a third of all US doctors agreed that cigarette smoking should be considered 'a major cause of lung cancer'. This same poll revealed that 43% of all American doctors were still smoking cigarettes on a regular basis, with occasional users accounting for another 5%.[31] With half of all doctors smoking, it should come as no surprise that most Americans remained unconvinced of life-threatening harms from the habit.

The tobacco industry was not innocent in this persistence of ignorance. Cigarette makers spent countless sums to deny and distract from the cigarette–cancer link, in some instances actually quantifying the impact of their denialist propaganda. In 1973, for example, the Tobacco Institute hired AHF-Basico Market Research Co. and Audience Studies, Inc., to measure the impact of its 1972 propaganda film, 'Smoking and Health: The Need to Know', shown to hundreds of thousands throughout the country, including high school students. Prior to screening, viewers were asked a series of questions about whether the Surgeon General 'could be wrong about the dangers of smoking'; the same questions were then asked after the screening. Anne Duffin at the Tobacco Institute was happy to report that the film had reduced by 17.8% the number of people agreeing that 'Cigarette smoking cause[s] lung cancer' (from 74.9% to 57.1%). The film had also produced 'significant shifts' in attitudes favourable to the industry in other areas, including whether recent reports had 'overemphasized the dangers of smoking'.[32]

Global denialist campaigns have borne similar fruit. In the 1980s, UK tobacco researchers commented on how Philip Morris was piloting a 'global strategy' to deny the reality of secondhand smoke hazards, spending vast sums of money 'to keep the controversy alive'.[33] Hundreds of millions of Chinese remain poorly informed about the hazards of smoking, and as recently as 2011, scholars from the International Tobacco Control Policy Evaluation Project in The Netherlands published a survey showing that only 61 per cent of Dutch adults agreed that cigarette smoke endangered non-smokers.[34]

THE GLOBAL TOLL

The cigarette is the deadliest artefact in the history of human civilisation.[21] Consumption rates are falling in most of the richer

countries, but smoking rates remain high or even increasing in many parts of the globe. In China, cigarette consumption has risen from about 500 billion 1980 to over four times that in 2010, and it is not yet clear whether consumption has peaked. China is now manufacturing about 2.4 trillion cigarettes per year, close to 40% of the global total. Consumption has been facilitated by the introduction of ultra high speed cigarette making machines: Hongta's Yuxi Cigarette Factory, for example, produces over 90 billion cigarettes per year, using 52 high-speed Molins cigarette making machines. Modern cigarette making machines of the sort made by the Hauni Corporation in Hamburg or GD (Generate Differences) in Bologna crank out cigarettes at rates up to 20 000 per min, which helps account for the dramatic drop in manufacturing costs over the last century or so. Cigarette factories today produce death at a faster rate—and cheaper—than any previous form of industrial manufacture. If cigarettes cause 1 lung cancer for every 3 or 4 million smoked,[35] this means that a factory such as Hongta's in Yuxi is responsible for generating 25 000 or 30 000 deaths per year from lung cancer. And about twice that number from other diseases. There are about 400 industrial-scale cigarette factories in the world,[36] each of which causes thousands of preventable deaths per year (see box 1 and table 1).

There are still many myths surrounding smoking—that the dangers have long been 'common knowledge', for example, or that legitimate scholarly doubt about the reality of hazards postdates the Surgeon General's report of 1964.[37–39] Yet another myth, though, is that the tobacco 'problem' has by and large been 'solved'. Tobacco is commonly referred to in the past tense—as when critics of the fast food industry talk about solving dietary problems 'the way the tobacco problem was solved'. The fact is that cigarette use persists, and on a massive scale. Global cigarette use seems to have peaked at about 6 trillion cigarettes sometime after the turn of the new millennium, but the deadly effects of this epidemic will still be felt for decades—even if global use continues to decline. Only about 100 million people died from smoking in the 20th century, whereas several times that are likely to die in the present century, even if current rates of smoking fall dramatically.[35] Most of the tobacco epidemic remains in the future, with the total global toll likely to approach 2 million lung cancer deaths per year in the 2020s or 2030s.

No causes are themselves uncaused, however, which means that when we think about what causes lung cancer or even smoking, we should think not just in terms of how individuals 'decide' to start smoking, but rather in terms of larger, more weblike threads of causation. We have to look at the cigarette epidemic—and therefore lung cancer—as facilitated by long causal chains of a sociopolitical, technical, molecular and agricultural nature. If cigarettes cause cancer, then so do the machines that roll cigarettes and the companies that supply the 'filters', 'flavourants' and paper. We have to realise that adverts can be carcinogens, along with the convenience stores and pharmacies that sell cigarettes. The executives who work for cigarette companies cause cancer, as do the artists who design cigarette packs and the PR and advertising firms that manage such accounts. Farmers who grow tobacco are part of this

Box 1 What is a human life worth to a cigarette manufacturer?

Cigarettes cause about one death per million smoked[35] with a latency of about 25 years, which is why the 6 trillion smoked in 1990 will cause about 6 million deaths in 2015. That's one death every 5 seconds. One-third or one-quarter of those deaths will be from lung cancer; about one every 15 or 20 s.

This relationship is fairly consistent in different parts of the world, given the homogeneity of cigarettes and how similarly they are smoked. It also means we can generate some interesting equivalences. Cigarettes typically come in 20 sticks per pack, with 200 sticks per carton, 10 000 sticks per master case and 10 million sticks per container. A 12 m (40 ft) container of the sort shipped overseas or trucked by highway houses 10 million cigarettes, which means that each container will cause about 10 deaths.

We can also think about this in terms of the rate at which cigarettes are smoked. A total of 6 trillion cigarettes are smoked every year, and if each cigarette is about 60 mm (counting only the part that is smoked), this means that 360 trillion mm of cigarettes are smoked per year. Converting this, 360 trillion mm is 360 billion m, or 360 million km. Imagined as one long rod, this means that cigarettes are smoked at a rate of 360 million km per year, which is more than 10 km/s. Cigarettes are smoked at a rate equal to the speed at which satellites orbit the earth.

We can also think about the deaths caused per unit weight of stuffing. Cigarettes contain about two-thirds of a gram of tobacco, which means that if it takes 3 million cigarettes to cause one lung cancer, it takes about 2 million g—or 2 metric tonnes—to cause one lung cancer. A typical tobacco farm yields about 2 tonnes per hectare, so a 10-hectare field will cause about 10 lung cancer deaths/year. And 20 additional deaths from heart attacks, gangrene of the feet, cancers of the bladder and oral cavity, etc.

Finally, we can also think about this in terms of the value of a life as assumed by tobacco manufacturers. Cigarette companies make about a penny in profit for every cigarette sold, or about US $10 000 for every million cigarettes purchased. Since there is one death for every million cigarettes sold (or smoked), a tobacco manufacturer will make about US$10 000 for every death caused by their products. Otherwise put: a cigarette manufacturer will not forgo US$10 000 in profit, even if this means the death of one of their customers. The value of a human life to a cigarette manufacturer is therefore about US$10 000.

Table 1 Factories of death (selected)

	Cigarettes produced/ year (year)	Deaths caused per year
Philip Morris's Richmond plant	146 billion (2010)	146 000
Philip Morris Holland, Bergen op Zoom, The Netherlands	96 billion (2006)	96 000
Yuxi Cigarette Factory, Yunnan	90 billion (2008)	130 000
Kunming Cigarette Factory, Kunming, China	71 billion (2010)	71 000
Philip Morris Izhora Cigarette Factory, St. Petersburg	70 billion (2011)	70 000
Hong He Cigarette Factory, Yunnan, China	65 billion (2005)	65 000
Anyang Cigarette Factory, China	50 billion (2008)	50 000
Hongyun Cigarette Factory, Qujing, Yunnan	47 billion (2008)	47 000
Thane Road, Nottingham (Imperial Tobacco), UK	50 billion (2003)	50 000
Hangzhou Cigarette Factory, China	47 billion (2007)	47 000
Reemtsma, Berlin	36 billion (2005)	36 000
Philip Morris Kuban, Russia	33 billion (2002)	33 000

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What this paper adds

- This paper reviews the converging lines of evidence that led to the recognition that smoking is the major cause of lung cancer.
- It also shows that the non-scholarly public was slower than scholars and medical professionals to recognise tobacco harms.
- The point is made that part of that lag can be traced to campaigns mounted by the industry to manufacture doubt.
- The point is also made that global tobacco use would be declining were it not for China, which now accounts for about 40 percent of all cigarettes sold (and smoked).
- Deaths caused by some of the world's largest tobacco factories are calculated, and the value of a human life for a cigarette manufacturer is shown to be about $10 000.

network, as are the politicians who take money from 'Big Tobacco', and those chemists and breeders who favour the nicotine molecule. So too must we include those many hundreds of experts who testify for the industry in court.[21] We need to better understand such webs or networks if we are to be more creative in finding ways to reduce the toll from this, the world's deadliest malignancy.

Competing interests The author has served as an expert witness in litigation against the tobacco industry.

Provenance and peer review Commissioned; externally peer reviewed.

REFERENCES

1. **IARC Globocan 2008.** *Cancer Fact Sheet: Lung Cancer Mortality Worldwide in 2008.* http://globocan.iarc.fr/factsheets/cancers/lung.asp
2. **Adler I.** *Primary Malignant Growths of the Lungs and Bronchi.* London: Longmans, 1912:22.
3. **Ochsner A.** My first recognition of the relationship of smoking and lung cancer. *Prev Med* 1973;**2**:611–14.
4. **Müller FH.** Tabakmissbrauch und Lungencarcinom. *Zeitschrift für Krebsforschung* 1939;**49**:57–85.
5. **Schairer E,** Schöniger E. Lungenkrebs und Tabakverbrauch. *Zeitschrift für Krebsforschung* 1943;**54**:261–9.
6. **Doll R,** Hill AB. The mortality of doctors in relation to their smoking habits. *BMJ* 1954;**1**:1451–5.
7. **Hammond EC,** Horn D. The relationship between human smoking habits and death rates: a follow-up study of 187,766 men. *JAMA* 1954;**155**:1316–28.
8. **Ubell E.** *Cigarette—Lung Cancer Link Proved, Dr Hammond Says.* Herald Tribune, 1954. http://legacy.library.ucsf.edu/tid/zke6aa00
9. **Brosch A.** Theoretische und experimentelle Untersuchungen zur Pathogenesis und Histogenesis der malignen Geschwülste. *Virchows Arch B Cell Pathol* 1900;**162**:32–84.
10. **Roffo AH.** Durch Tabak beim Kaninchen entwickeltes Carcinom. *Zeitschrift für Krebsforschung* 1931;**33**:321.
11. **Proctor RN.** *The Nazi War on Cancer.* Princeton: Princeton University Press, 1999.
12. **Wynder E,** Graham EA, Croninger AB. Experimental production of carcinoma with cigarette tar. *Cancer Res* 1953;**13**:855–66.
13. *Beyond Any Doubt. Time* 1953:60–3.
14. **Lewton LC.** Substances present in tobacco smoke which are irritating to the nose and their removal by a new process. 1932. http://legacy.library.ucsf.edu/tid/cub54f00
15. **Hilding AC.** On cigarette smoking, bronchial carcinoma and ciliary action. *New Engl J Med* 1956;**254**:1155–60.
16. **Auerbach O,** Forman JB, Gere JB, *et al.* Changes in the bronchial epithelium in relation to smoking and cancer of the lung. *New Engl J Med* 1957;**256**:97–104.
17. **Roffo AH.** Krebserzeugendes Benzpyren gewonnen aus Tabakteer. *Zeitschrift für Krebsforschung* 1939;**49**:588–97.
18. **Fishel JB.** *Study of Cigarette Smoke.* Lorillard, 1947. http://legacy.library.ucsf.edu/tid/esa20e00
19. **Brown & Williamson.** *"Report of Progress—Technical Research Department" (B&W).* 1952:8. http://legacy.library.ucsf.edu/tid/aql66b00
20. **Wakeham H.** *Tobacco and Health—R&D Approach.* Philip Morris, 1961:9. http://legacy.library.ucsf.edu/tid/mdd35d00
21. **Proctor RN.** *Golden Holocaust: Origins of the Cigarette Catastrophe and the Case for Abolition.* Berkeley: University of California Press, 2011.
22. **Teague CE.** *Survey of Cancer Research.* Reynolds, 1953. http://legacy.library.ucsf.edu/tid/jad76b00
23. *Parmele HB to Riafner A.* Lorillard, 1946. http://legacy.library.ucsf.edu/tid/tgt34c00/pdf
24. **Dakin EF.** *Forwarding Memorandum: To Members of the Planning Committee.* Hill & Knowlton, 1953:2. http://legacy.library.ucsf.edu/tid/gyn66b00
25. **Bentley HR,** Felton DGI, Reid WW. *Report on visit to U.S.A. and Canada.* 1958:2. http://legacy.library.ucsf.edu/tid/xro56b00
26. **Rodgman A.** *The Smoking and Health Problem: A Critical and Objective Appraisal.* 1962:7. http://legacy.library.ucsf.edu/tid/iis76b00
27. **Proctor RN.** *Trial testimony in Ironworkers v. Philip Morris.* 1999. http://legacy.library.ucsf.edu/tid/ejg35a00
28. **Cameron CS.** *Lung Cancer and Smoking: What We Really Know.* Atlantic Monthly, 1956:75.
29. **Proctor RN,** Schiebinger L, eds. *Agnotology: The Making and Unmaking of Ignorance.* Stanford: Stanford University Press, 2008.
30. **Gallup GH.** *The Gallup Poll: Public Opinion 1935-71,* **vol. 2.** New York: Random House, 1972. http://legacy.library.ucsf.edu/tid/qpb42c00
31. **Tegan J.** *Many Doctors Link Smoking and Cancer.* Washington Daily News, 1960. http://legacy.library.ucsf.edu/tid/scv02a00
32. *Duffin A to Kloepfer W. Audience testing of "Smoking & Health: The Need to Know."* 1973. http://legacy.library.ucsf.edu/tid/uqn92f00
33. **Boyse S.** *Note on a Special Meeting of the UK Industry on Environmental Tobacco Smoke.* London: BAT, 1988. http://legacy.library.ucsf.edu/tid/dof53a00
34. **ITC Project.** *ITC Netherlands Survey. Report on Smokers' Awareness of the Health Risks of Smoking and Exposure to Second-hand Smoke.* Ontario, Canada: University of Waterloo, 2011.
35. **Proctor RN.** Tobacco and the global lung cancer epidemic. *Nat Rev Cancer* 2001;**1**:82–6.
36. **Kohrman M.** Cigarette citadels: the map project. https://www.stanford.edu/group/tobaccoprv/cgi-bin/wordpress/
37. **Proctor RN.** "Everyone knew but no one had proof": Tobacco industry use of medical history expertise in US courts, 1990-2002. *Tob Control* 2006;**15**:iv117–25.
38. **Brandt AM.** *The Cigarette Century: The Rise, Fall, and Deadly Persistence of the Product that Defined America.* New York: Basic Books, 2007.
39. **Kyriakoudes L.** "Historians' testimony on 'common knowledge' of the risks of tobacco use: a review and analysis of experts testifying on behalf of cigarette manufacturers in civil litigation." *Tob Control* 2006;**15**:iv107–16.

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The history of the discovery of the cigarette–lung cancer link: evidentiary traditions, corporate denial, global toll

Robert N Proctor

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Correction

Proctor RN. The history of the discovery of the cigarette–lung cancer link: evidentiary traditions, corporate denial, global toll. *Tob Control* 2012;**21**:87-91. The data related to 'Yuxi Cigarette Factory, Yunnan' in Table 1 was misprinted. The correct table should appear as below:

Table 1 Factories of death (selected)

	Cigarettes produced/year (year)	Deaths caused per year
Philip Morris's Richmond plant	146 billion (2010)	146 000
Philip Morris Holland, Bergen op Zoom, The Netherlands	96 billion (2006)	96 000
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Editorials

Evidence based medicine: what it is and what it isn't

It's about integrating individual clinical expertise and the best external evidence

Evidence based medicine, whose philosophical origins extend back to mid-19th century Paris and earlier, remains a hot topic for clinicians, public health practitioners, purchasers, planners, and the public. There are now frequent workshops in how to practice and teach it (one sponsored by the BMJ will be held in London on 24 April); undergraduate[1] and postgraduate[2] training programmes are incorporating it[3] (or pondering how to do so); British centres for evidence based practice have been established or planned in adult medicine, child health, surgery, pathology, pharmacotherapy, nursing, general practice, and dentistry; the Cochrane Collaboration and Britain's Centre for Review and Dissemination in York are providing systematic reviews of the effects of health care; new evidence based practice journals are being launched; and it has become a common topic in the lay media. But enthusiasm has been mixed with some negative reaction.[4,5,6] Criticism has ranged from evidence based medicine being old hat to it being a dangerous innovation, perpetrated by the arrogant to serve cost cutters and suppress clinical freedom. As evidence based medicine continues to evolve and adapt, now is a useful time to refine the discussion of what it is and what it is not.

Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research. By individual clinical expertise we mean the proficiency and judgment that individual clinicians acquire through clinical experience and clinical practice. Increased expertise is reflected in many ways, but especially in more effective and efficient diagnosis and in the more thoughtful identification and compassionate use of individual patients' predicaments, rights, and preferences in making clinical decisions about their care. By best available external clinical evidence we mean clinically relevant research, often from the basic sciences of medicine, but especially from patient centred clinical research into the accuracy and precision of diagnostic tests (including the clinical examination), the power of prognostic markers, and the efficacy and safety of therapeutic, rehabilitative, and preventive regimens. External clinical evidence both invalidates previously accepted diagnostic tests and treatments and replaces them with new ones that are more powerful, more accurate, more efficacious, and safer.

Good doctors use both individual clinical expertise and the best available external evidence, and neither alone is enough. Without clinical expertise, practice risks becoming tyrannised by evidence, for even excellent external evidence may be inapplicable to or inappropriate for an individual patient. Without current best evidence, practice risks becoming rapidly out of date, to the detriment of patients.

This description of what evidence based medicine is helps clarify what evidence based medicine is not. Evidence based medicine is neither old hat nor impossible to practice. The argument that "everyone already is doing it" falls before evidence of striking variations in both the integration of patient values into our clinical behaviour[7] and in the rates with which clinicians provide interventions to their patients.[8] The difficulties that clinicians face in keeping abreast of all the medical advances reported in primary journals are obvious from a comparison of the time required for reading (for general medicine, enough to examine 19 articles per day, 365 days per year[9]) with the time available (well under an hour a week by British medical consultants, even on self reports[10]).

The argument that evidence based medicine can be conducted only from ivory towers and armchairs is refuted by audits from the front lines of clinical care where at least some inpatient clinical teams in general medicine,[11] psychiatry (J R Geddes et al, Royal College of Psychiatrists winter meeting, January 1996), and surgery (P McCulloch, personal communication) have provided evidence based care to the vast majority of their patients. Such studies show that busy clinicians who devote their scarce reading time to selective, efficient, patient driven searching, appraisal, and incorporation of the best available evidence can practice evidence based medicine.

Evidence based medicine is not "cookbook" medicine. Because it requires a bottom up approach that integrates the best external evidence with individual clinical expertise and patients' choice, it cannot result in slavish, cookbook approaches to individual patient care. External clinical evidence can inform, but can never replace, individual clinical expertise, and it is this expertise that decides whether the external evidence applies to the individual patient at all and, if so, how it should be integrated into a clinical decision. Similarly, any external guideline must be integrated with individual clinical expertise in deciding whether and how it matches the patient's clinical state, predicament, and preferences, and thus whether it should be applied. Clinicians who fear top down cookbooks will find the advocates of evidence based medicine joining them at the barricades.

Some fear that evidence based medicine will be hijacked by purchasers and managers to cut the costs of health care. This would not only be a misuse of evidence based medicine but suggests a fundamental misunderstanding of its financial consequences. Doctors practising evidence based medicine will identify and apply the most efficacious interventions to maximise the quality and quantity of life for individual patients; this may raise rather than lower the cost of their care.

Evidence based medicine is not restricted to randomised trials and meta-analyses. It involves tracking down the best external evidence with which to answer our clinical questions. To find out about the accuracy of a diagnostic test, we need to find proper cross sectional studies of patients clinically suspected of harbouring the relevant disorder, not a randomised trial. For a question about prognosis, we need proper follow up studies of patients assembled at a uniform, early point in the clinical course of their disease. And sometimes the evidence we need will come from the basic sciences such as genetics or immunology. It is when asking questions about therapy that we should try to avoid the

non-experimental approaches, since these routinely lead to false positive conclusions about efficacy. Because the randomised trial, and especially the systematic review of several randomised trials, is so much more likely to inform us and so much less likely to mislead us, it has become the "gold standard" for judging whether a treatment does more good than harm. However, some questions about therapy do not require randomised trials (successful interventions for otherwise fatal conditions) or cannot wait for the trials to be conducted. And if no randomised trial has been carried out for our patient's predicament, we must follow the trail to the next best external evidence and work from there.

Despite its ancient origins, evidence based medicine remains a relatively young discipline whose positive impacts are just beginning to be validated,[12] [13] and it will continue to evolve. This evolution will be enhanced as several undergraduate, postgraduate, and continuing medical education programmes adopt and adapt it to their learners' needs. These programmes, and their evaluation, will provide further information and understanding about what evidence based medicine is and is not.

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---

1. British Medical Association. Report of the working party on medical education. London: BMA, 1995.

2. Standing Committee on Postgraduate Medical and Dental Education. Creating a better learning environment in hospitals. 1. Teaching hospital doctors and dentists to teach. London: SCOPME, 1994.

3. General Medical Council. Education committee report. London: GMC, 1994.

4. Grahame-Smith D. Evidence based medicine: Socratic dissent. *BMJ* 1995;310:1126-7. [Free Full Text]

5. Evidence based medicine; in its place [editorial]. *Lancet* 1995;346:785. [Medline]

6. Correspondence. Evidence based medicine. *Lancet* 1995;346:1171-2.

7. Weatherall DJ: The inhumanity of medicine. BMJ 1994;309;1671-2.

8. House of Commons Health Committee. Priority setting in the NHS: purchasing. First report sessions 1994-95. London: HMSO, 1995. (HC 134-1.)

9. Davidoff F, Haynes B, Sackett D, Smith R. Evidence based medicine: a new journal to help doctors identify the information they need. *BMJ* 1995;310:1085-6. [Free Full Text]

10. Sackett DL. Surveys of self-reported reading times of consultants in Oxford, Birmingham, Milton-Keynes, Bristol, Leicester, and Glasgow. In: Rosenberg WMC, Richardson WS, Haynes RB, Sackett DL. Evidence-based medicine. London: Churchill Livingstone (in press).

11. Ellis J, Mulligan I, Rowe J, Sackett DL. Inpatient general medicine is evidence based. *Lancet* 1995;346:407-10. [Medline]

12. Bennett RJ, Sackett DL, Haynes RB, Neufeld VR. A controlled trial of teaching critical appraisal of the clinical literature to medical students. *JAMA* 1987;257:2451-4. [Abstract]

13. Shin JH, Flaynes RB, Johnston ME. Effect of problem-based, self-directed undergraduate education on life-long learning. *Can Med Assoc J* 1993;148:969-76. [Abstract]

Related Article

Evidence based medicine: does it make a difference?: Use wisely

Benjamin Druss

BMJ 2005 330: 92. [Extract] [Full Text]

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ELECTROMAGNETIC FIELD SENSITIVITY

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ABSTRACT

A multiphase study was performed to find an effective method to evaluate electromagnetic field (EMF) sensitivity of patients. The first phase developed criteria for controlled testing using an environment low in chemical, particulate, and EMF pollution. Monitoring devices were used in an effort to ensure that extraneous EMF would not interfere with the tests. A second phase involved a single-blind challenge of 100 patients who complained of EMF sensitivity to a series of fields ranging from 0 to 5 MHz in frequency, plus 5 blank challenges. Twenty-five patients were found who were sensitive to the fields, but did not react to the blanks. These were compared in the third phase to 25 healthy naive volunteer controls. None of the volunteers reacted to any challenge, active or blank, but 16 of the EMF-sensitive patients (64%) had positive signs and symptoms scores, plus autonomic nervous system changes. In the fourth phase, the 16 EMF-sensitive patients were rechallenged twice to the frequencies to which they were most sensitive during the previous challenge. The active frequency was found to

be positive in 100% of the challenges, while all of the placebo tests were negative. We concluded that this study gives strong evidence that electromagnetic field sensitivity exists, and can be elicited under environmentally controlled conditions.

INTRODUCTION:

Interaction mechanisms that underlie the health and biological effects of electromagnetic fields (EMF) on humans have been studied by many authors (1,2,3,4,5,6). This subject was reviewed recently at the 1990 Spring Meeting of the American Physical Society (7). Choy *et. al.* (8) investigated individuals with multiple sensitivities who reported reactions to various types of electrical equipment, including power lines, electronic office equipment such as typewriters and computer terminals, video display terminals, household appliances (such as hair dryers), and fluorescent lights.

This paper presents preliminary data on electromagnetic field tests using a square wave generator to evaluate the EMF sensitivity of patients reporting such sensitivities under environmentally controlled and monitored conditions.

MATERIALS AND METHODS:

This study has been carried out in four phases.

I. The tests were carried out in an environmentally controlled area with porcelain-on-steel walls to minimize airborne chemical pollution which might interfere with the testing procedure. This type of construction also acted to decrease external electromagnetic fields. Portable EMF monitoring devices were used to find an area that would minimize background EMF which might disturb double-blind challenges and interfere with the testing process. The low-pollution room had a background of 0-100 V/m electric field and 20-200 nT (Tesla) magnetic field. The immediate test site of the patients had unmeasurable electrical fields and magnetic fields in the vicinity of 20 nT.

The major emphasis of this phase of the studies was the evaluation of the effects of the magnetic field generated by a coil fed from a sweep/function generator (Model 3030, B.K. Precision Dynascan Corp.). This equipment allowed us to test square wave frequencies from 0.1 Hz to 5 MHz.

The patients were tested while they were sitting comfortably upright in a chair with the generator on a desk at least 2 m away,

with its output connected to a coil 6 cm in diameter and 15 cm tall, made of 35 m of cable and positioned on the floor with its center approximately 0.3 m from the feet of the person tested. The mean values of the alternating magnetic field generated by this arrangement were approximately 2900 nT at floor level, approximately 350 nT at the level of the chair seat and patients' knees, and about 70 nT at hand level. The exposure period lasted approximately 3 minutes per challenge.

Before the EMF challenge, blood pressure, pulse rate, respiratory rate, temperature, sign and symptom scores, and autonomic nervous system functions were tested. The autonomic nervous system function was tested with a binocular iriscorder (Model C2515, Hamamatsu Photonics), which measured pupil area, time at which constriction and dilation occurred, and rate of constriction/dilation (9).

All patients had been previously evaluated and treated for biological inhalant, food and chemical sensitivities in order to minimize possible confusion from coexisting problems. The patients were stabilized on a healthy diet in a constant low-pollution environment. In addition, they had their overall body load reduced and stabilized in a controlled environment.

II. This was a single-blind screening of 100 patients who complained of being EMF-sensitive. They were challenged under low-pollution conditions using the sweep/function generator at 0.1, 0.5, 1, 2.5, 5, 10, 20, 40, 50, 60, and 100 Hz; then at 1, 5, 10, 20, 35, 50, 75, and 100 KHz; and finally at 1 and 5 MHz. There were twenty-one active challenges and five blanks (placebos) per person, giving a total of 2600 challenges. When the number and/or intensity of symptoms were 20% over baseline, the result was considered positive, and were recorded as such under the various criteria used. A change in the iriscorder readings more than two standard deviations from baseline was also recorded as a positive result.

III. Twenty-five patients, who were found to be positive in phase II challenges, and who had no more than one placebo reaction were then selected for a third phase of the study. In addition, 25 healthy naive volunteers were challenged. Double-blind EMF challenges and placebos using the aforementioned parameters were performed. There were 1300 total challenges, of which 1050 were

Table 1

Phase II — Single-blind Challenge of 100 Patients

No. of Patients	No. of Active Challenges	No. of Blank Challenges	Pos. Reactions to Active Challenges	Pos. Reactions to Blanks
50	1050	250	750	150
25	525	125	0	0
25	525	125	325	0

active and 250 were blanks. The tests averaged 21 active frequencies and 5 blanks per subject.

IV. Sixteen patients who reacted in phase III were then rechallenged on two separate occasions in a double-blind manner, using only the frequencies to which they had responded most strongly. For each subject, the frequency of maximum sensitivity was inserted randomly into a series of 5 placebo challenges. Thus, there were a total of 32 active challenges and 160 blanks.

RESULTS:

Phase I. The EMF measurements were quite reproducible. We found that the lights and air handling equipment had to be off during the tests because of their electromagnetic field output. Baseline studies on patients were completed without remarkable result.

Phase II. Of the total of 100 patients tested in the single-blind study, 50 reacted to several of the placebos in addition to the active challenges, and were excluded from further study. Twenty-five subjects who did not react to any active challenges were also excluded. A final 25 subjects who did react to active challenges, but not to blanks, were selected for the third phase of the study (Table 1).

Phase III. The 25 subjects selected from phase II were rechallenged, and 16 (64%) reacted positively to the active challenges

(Table 2). The total number of positive reactions to the 336 active challenges in the 16 patients was 179 (53%), as compared to 6 positive reactions out of 80 blanks (7.5%). There were no reactions to any challenge, active or placebo, in the volunteer group of naive subjects (Table 2).

When evaluating frequency response, 75% of the 16 patients reacted to 1 Hz, 75% to 2.5 Hz, 69% to 5 Hz, 69 % to 10 Hz, 69% to 20 Hz, and 69% to 10 KHz (Table 3). No patient reacted to all 21 of the active frequencies in the challenges. The average was 11 reactive frequencies per patient, with a range of 1 to 19 positive responses.

The principal signs and symptoms produced were neurological (tingling, sleepiness, headache, dizziness, unconsciousness), musculoskeletal (pain, tightness, spasm, fibrillation), cardiovascular (palpitation, flushing, tachycardia, edema), oral/respiratory (pressure in ears, tooth pain, tightness in chest, dyspnea), gastrointestinal (nausea, belching), ocular (burning), and dermal (itching, burning, prickling pain) (Table 4). Most reactions were neurological.

Phase IV. In the 16 patients again rechallenged in a double-blind manner, using only the single frequency to which they were most sensitive, all reported reactions to the active frequencies when challenged. None reacted to the placebos (Table 5). Signs and symptoms in all 16 patients were positive as was the autonomic nervous system dysfunction, as measured by the iriscorder (Table 6, Figure 1). Examples of changes were a 20% decrease in pulmonary function and a 40% increase in heart rate. In the 16 patients with positive reactions to EMF challenges, two had delayed reactions; gradually became depressed and finally became unconscious. Eventually, they awoke without treatment. Symptoms lasted from 5 hours to 3 days.

DISCUSSION:

Since it has been found that electromagnetic fields can affect health, researchers have investigated these phenomena *in vivo* and *in vitro*, in animals (10,11,12) and humans (1,2,3,4,5,6,7).

No individual had been specifically challenged in an attempt to reproduce acute symptoms until Smith and Monro (5) followed by

Table 2

Phase III - 25 Patients Previously Positive Rechallenged And Twenty-Five Controls Tested Double-blind

No. of Persons	No. of Active Challenges	No. of Blank Challenges	Positive Reactions to Challenges	Positive Reactions to Blanks
16 patients (out of 25 reacting positively)	336	80	179	6
25 controls (none of them reacting positively)	525	125	0	0

Table 3

PERCENTAGE OF 16 PATIENTS WITH POSITIVE REACTION TO DIFFERENT FREQUENCIES

Frequency (Hz)	Patients with Positive Reaction %
0.1	31
0.5	44
1	75
2.5	75
5	69
10	69
20	69
40	50
50	50
60	63
100	56
1K	56
5K	38
10K	69
20K	56
35K	31
50K	50
75K	50
100K	38
1M	50
5M	31

Table 4
Comparison of Symptoms and Signs Induced by Frequencies

Hz.	No. patients w/pos.reaction	Neurological No.of Pts. %	Musculoskeletal No.of Pts. %	Cardiovascular No.of Pts. %	Respiratory No.of Pts. %	Gastrointestinal No.of Pts. %	Eyes No.of Pts. %	Skin No.of Pts. %
0.1	5	3 60	0 0	0 0	0 0	1 20	0 0	0 0
0.5	7	4 57	0 0	0 0	0 0	0 0	0 0	0 0
1	12	4 33	3 25	0 0	1 8	1 8	0 0	0 0
2.5	12	5 42	2 17	0 0	1 8	1 8	0 0	0 0
5	11	5 46	0 0	1 9	2 18	1 9	0 0	0 0
10	11	7 64	1 9	0 0	2 18	0 0	0 0	0 0
20	11	4 36	0 0	1 9	1 9	1 9	0 0	0 0
40	8	4 50	0 0	0 0	2 25	0 0	0 0	1 13
50	8	5 63	0 0	2 25	1 13	0 0	0 0	0 0
60	10	5 50	0 0	1 10	3 30	0 0	0 0	0 0
100	9	4 44	0 0	1 11	2 22	1 11	0 0	0 0
1K	9	6 67	0 0	1 11	0 0	0 0	1 11	0 0
5K	6	2 33	1 17	0 0	1 17	0 0	0 0	0 0
10K	11	4 36	1 9	0 0	0 0	0 0	0 0	0 0
20K	9	5 56	0 0	2 22	0 0	0 0	0 0	1 11
35K	5	2 40	0 0	0 0	1 20	0 0	0 0	1 20
50K	8	2 25	0 0	1 13	2 25	0 0	0 0	1 13
75K	8	1 13	0 0	1 13	3 38	0 0	1 13	0 0
100K	6	2 33	2 33	0 0	2 33	0 0	0 0	0 0
1M	8	4 50	1 13	0 0	0 0	0 0	0 0	0 0
5M	5	2 40	1 20	0 0	0 0	0 0	0 0	0 0

179 positive reactions out of 336 individual challenges

Table 5

Phase IV --Sixteen Patients Rechallenged to One Active Frequency on Two Separate Episodes and in Addition to Five Blank Challenges on Each Episodes -- Double-blind

First Episode of Challenge

No. of patients	Total No. of frequencies	Total No. of blanks	No. of patients reacting to active challenge	No. of patients reacting to blanks
16	16	80	16	0

Second Episode of Challenge

No. of patients	Total No. of frequencies	Total No. of blanks	No. of patients reacting to active challenge	No. of patients reacting to blanks
16	16	80	16	0

Choy, Monro, and Smith (8), who used a series of oscillators of varying frequency to trigger symptoms in electrically sensitive patients. We modified this procedure by developing controlled environmental areas where baselines were constantly monitored for particulates, pollutants, and extraneous fields. Here, controlled EMF output was applied so that data would be more reproducible.

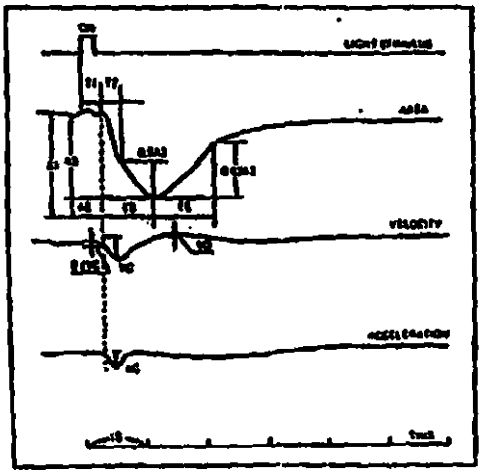
Several factors have led us to believe that we have reproducible results. Meticulous construction of environmental rooms made a great difference in the reproducibility of test results. Prior to the use of such facilities and careful monitoring, a variety of factors, such as diet, exposure to chemicals, EMF, or dust gave rise to symptoms which would have been mistaken for placebo reactions. Such effects were minimized here, as evidenced by the small number of placebo reactions. A few patients reacted to the fields generated by the monitoring devices (Iriscorder, EKG, and computers) and had to be dropped from the study as too fragile for accurate analysis. Some patients reacted to the fields generated by the fluorescent lights, and others did not present the same

Table 6

Parameters of 25 normal control's pupillary light reflex - Iriscorder - EEC-Dallas (Right and Left Eyes Combined)

Parameter	x ± SD	Percent Variation
A1	5.70 ± 3.58	10.0
CR	0.46 ± 0.048	10.4
T2	190.74 ± 18.36	9.5
VC	49.67 ± 5.86	11.8
AC	503.20 ± 79.80	15.1
T5	1520.04 ± 286.86	18.7
VD	13.65 ± 2.44	17.9

Factors of Measured Value



The C2515 Iriscordor uses some or all of the following twelve factors to measure Light Reflex, Alternate-Stimulus Reflex, and Near Reflex.

A1 : Initial pupil area (mm^2)
A2 : Minimum pupil area after light stimulus (mm^2)
A3 : Pupil area change after light stimulus (mm^2)
CR: Contraction ratio (A2/A1)
D1 : Initial diameter ❶ (mm)
T1 : Time from light stimulus to start of contraction ❷ (msec)
T2 : Time to half contraction (msec)
T3 : Time to total contraction (msec)
T5 : Time to recover to 63% of A3 after dilation from minimum state (msec)
VC: Maximum velocity of contraction (mm^2/sec)
VD: Maximum velocity of dilation (mm^2/sec)
AC: Maximum acceleration of contraction (mm^2/sec^2)

❶ D1 is calculated from the pupil area, assuming that the pupil is circular.

❷ T1 is measured as the time from the light stimulus until the velocity of pupil contraction VC reaches 10% of the maximum velocity VCmax.

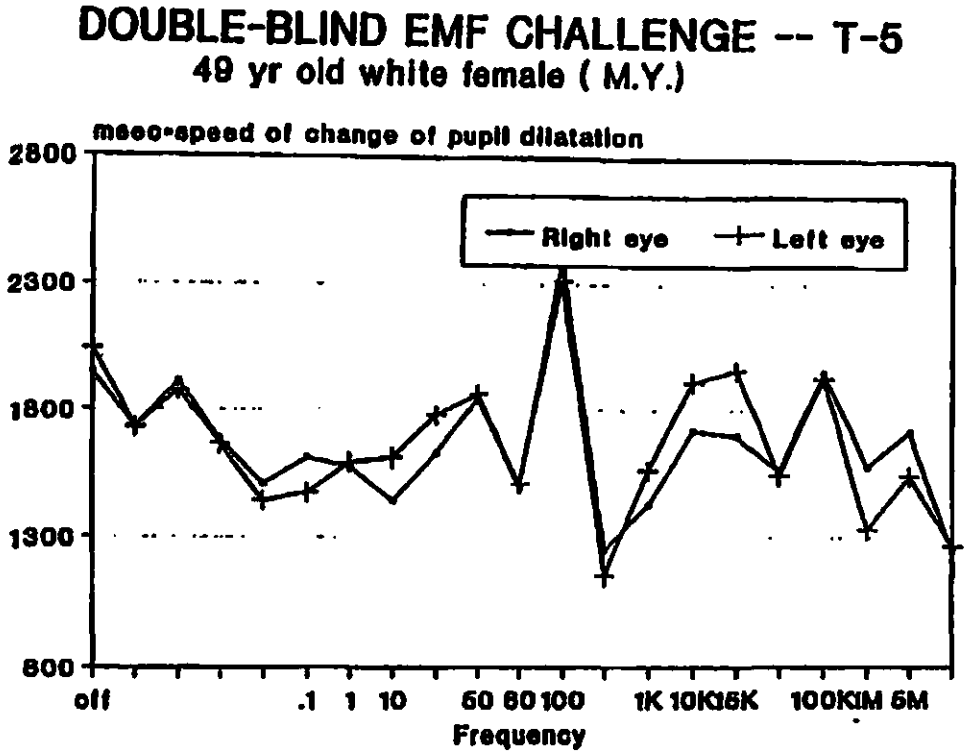


Figure 1. Speed of dilation of the pupil following EMF stimulation at various frequencies as measured by iriscorder. Note that right and left eyes respond simultaneously and to the same relative degrees at a given frequency. These results are quite reproducible (viz. text).

signs and symptoms at each challenge, even though the reactions were significant when contrasted with the blank responses. The Iriscorder data were objective, however, and were always reproducible (Figure 1).

We also noted that patients sometimes had delayed or prolonged responses. Therefore, care had to be taken to be certain that the patient had returned to baseline before the next challenge. This carry-over was first noted when evaluating responses to placebo

challenges. Such a response could usually be explained and eliminated by use of longer intervals between challenges.

In this study, of the 100 patients who expressed suspicion of EMF sensitivity, 75 actually responded to fields, whereas none of the controls did. Of the 75, 25 had no reactions to blanks, whereas 50 did, and thus were discarded from the study; even though we felt that some of the reactions to blanks might be evidence of delayed reaction to previous frequencies, or prolonged response to the previous positive challenge, as well as true placebo reactions.

We learned that challenge with 21 frequencies was impossible on many sensitive patients. They were often unwell for several hours or days, which confused the data from repeat challenges on subsequent days. Hence, we selected the one frequency of maximum sensitivity for repeat challenges in the phase IV studies.

When one compares the various groups to controls, it is clear that there is a group of patients who have unstable response systems which appear different from those of the individuals who acted as controls. These studies show that EMF sensitivity could be elicited under environmentally controlled conditions. As a result of the weak field levels and short exposure time, the responses were mild except in two patients whose symptoms were so severe (e.g. drop attack, severe itching) that they received intravenous vitamin C, magnesium, and oxygen as a result of the prolonged and delayed reactions.

Signs and symptoms appeared similar to those seen in food or chemically sensitive patients at the Environmental Health Center/ Dallas, and included neurological, musculoskeletal, cardiovascular, respiratory, gastrointestinal, dermal, and ocular changes. The neurological symptoms were most common. Similar responses have been recorded by others in the literature (5,6,7,8,13,14). In 1972, after the Soviets reported that electrical utility workers were suffering from listlessness, fatigue, and nausea, Subrahmangam and coworkers (13) investigated and reported decisive changes in cardiac function and biogenic levels when pulses of 0.01 and 0.1 Hz were used. They found significant changes in the hypothalamus in response to the EMF fields.

In these studies, the preponderance of reactions occurred at one to 10 Hz, which accords well with their observations. However, many reactions also occurred at 50 and 60 Hz, as well a some up to

5 MHz. We conclude that in any given individual, susceptibility may develop to any frequency, and produce reactions.

Static magnetic fields are known to cause increased blood pressure on some individuals (14). Choy and coworkers (8) found that EMF reactions in EMF sensitive patients were not limited to the nervous system, but occurred in the same systems as in these studies, which basically corroborate theirs, though neurological symptoms predominated in our experiments.

Over the past 30 years, numerous investigations with animals and a few epidemiological studies of human populations have been devoted to assessing the relationship of microwave exposure to cataract development. The severity and speed of formation depends not only on intensity, but also on wavelength and duration of exposure (16-21). McCally *et. al.* (22) reported damage to corneal epithelium in *Cynomolgus* monkeys after 2.45 GHz irradiation for several hours at only 20-30 mW/cm^2 (CW) or even 10-15 mW/cm^2 with pulsed fields. Therefore the results of Paz (23) strongly suggests that the potential for eye injury exists in surgery where EMF fields are present.

In our experience, the patients' clinical responses could not always be reproduced completely, but the objective Iriscorder, EKG, and respirometer could be. However, the responses were definitely different from controls or placebo challenges, In our experience over the years, we have found partial reproduction of symptoms on repeat challenge to be as significant as total reproduction. Therefore, significant differences from controls in objective measurements were deemed valid.

There are several explanations for lack of exact reproducibility. These are: a) the patients' total body loads were different at different exposure periods. For example, some patients may only respond to EMF when in a reactive hypersensitive state (5,8); b) tissue resistance could influence the effect of the EMF. Zimmerman (24) reported that electrical resistance of skin decreased with increasing temperature and increased with progressive drying, as might be expected; c) injections of antigen neutralizing substances prior to test may have reduced the response to EMF. One patient with asthma was sensitive to high voltage power lines a well as low voltage house wiring. He experienced muscle spasms in head, neck, arms, and legs. This patient was also

sensitive to dust, weeds, dust mites, and some foods. He reacted in our tests to 2.5 and 60 Hz, and to 5 and 50 KHz with tightness in the chest. He then received an antigen shot to neutralize his hypersensitivity reactions. Five months later, he was unreactive to EMF; d) weather changes might affect the results, since we know that the weather can influence the propagation of EMF, as may alterations in the geomagnetic fields. Since humidity, pollution, temperature, etc. can affect resistance and total body load, weather should perhaps affect the results. Adverse weather (inversions, for example) may increase pollution load, while good weather lessens it. There is some evidence of resonance between geomagnetic fields and an applied ac magnetic field (25), which implies that the results may depend in part at least upon the strength and orientation of the geomagnetic field in the test area; and e) different wave forms might cause different responses. In these experiments, we used only square wave inputs to the coils. Consequently, we do not know whether other wave forms (sine, sawtooth, triangular, etc.) might induce different types or intensities of reactions.

Thus far, definitive information has not been sufficient to identify a plausible mechanism for EMF interactions with biological tissue. Interactions appear to take place at the cell surface, perhaps acting on receptor sites and altering ion and molecular transport across the membranes (25). Further work remains to be done in the field.

It is clear that EMF sensitivity is a real phenomenon in some environmentally sensitive patients, because some had consistent reactions while none of the controls did. THis study must be considered as only preliminary, but the evidence clearly points to sensitivity in some people.

In conclusion, it is evident that EMF testing is at a rudimentary stage; but clearly EMF sensitivity exists and can be elicited under environmentally controlled conditions. Further studies are needed to investigate the effects of EMF fields on human health.

REFERENCES

1. Ravitz. L.J.: History, Measurement, and Applicability of Periodic Changes in the Electromagnetic Field in Health and Disease, Ann. N.Y. Acad. Sci. 98, 1144-1201, 1982.

2. Wever, R.A.: Human Circadian Rhythms Under the Influence of Weak Electric Fields and the Different Aspects of These Studies, Int. J. Biometeor. 17, 227-232, 1973.
3. Smith, C.W.: Superconducting Areas in Living Systems, in The Living State II, R.K. Mishra, ed., World Scientific, Singapore, 404-420, 1985.
4. Phillips, R.D.: Health Effects of ELF Fields: Research and Communications Regulation, Int'l. Utilities Symp., Toronto, Sept. 1986.
5. Smith, C.W., Jafarg-Asl, A.H., Choy, R.Y.S., and Monro, J.A.: The Emission of Low-Intensity Electromagnetic Radiation from Multiple Allergy Patients and other Biological Systems, in Proc. Int'l. Symp. on Photon Emission from Biological Systems, Wroclaw, Poland, B. Jezowska-Trzebiatowska, B. Kochel, J. Slawinski, and W. Streck, eds., World Scientific, Singapore, 110-126,
6. Ketchenm, E.E., Porter, W.E., and Bolton, N.E.: The Biological Effects of Magnetic Fields on Man, J. Am. Ind. Hyg. Assoc., 39, 1-11, 1978.
7. Smith, C.W., and Best, S.: Electromagnetic Man, St. Martins Press, New York, 1989.
8. Choy, R.V.S., Monro, J.A., and Smith, C.W.: Electrical Sensitivities in Allergy Patients, Clin. Ecol., 4, 93-102, 1986.
9. Shirakawa, S., Rea, W.J., Ishikawa, S., and Johnson, A.R.: Evaluation of the Autonomic Nervous System Response by Pupillographical Study in the Chemically Sensitive Patient
10. Microwave News, Sept./Oct., pp. 5,14, 1986.
11. Adey, R.W., Bawin, F.M., and Lawrence, A.F.: Effects of Weak Amplitude-Modulated Fields in Calcium Efflux from Awake Cat Cerebral Cortex, J. Bioelectromagnetics Soc., 3, 295-308, 1982.
12. Bullock, T.H.: Electromagnetic Sensing in Fish, Neurosci. Res. Program Bull., 15, 17-22, 1977.
13. Subrahmangam, S., Narayan, O.V.S., Porkodis, M., and Murugan, S.: Effect of ELF Magnetic Micropulsations on Physiology of Albino Rats, Int. J. BioMeteor., 29, 184-185, 1985.
14. Easterly, C.E.: Cardiovascular Risk from Exposure to Static magnetic Fields, J. Am. Ind. Hyg. Assoc., 41, 533-539, 1982.
15. Randegger, E.: Electromagnetic Pollution, Environ., 7, 22-26, 1988.
16. Silverman, C.: Epidemiological Studies of Microwave Effects, Proc. I.E.E.E., 68, 78-84, 1980.

17. Petersen, R.C.: Bioeffects of Microwaves; a Review of Current Knowledge, J. Occup. Med., 25, 103-111, 1980.
18. Birenbaum, L., Kaplan, L.T., Metaly, W., et. al.: Effect of Microwave on the Rabbit Eye, J. Microwave Pwr., 4, 232-243, 1969.
19. Michaelson, S.M.: Microwave Biological Overview, Proc. I.E.E.E., 68, 60-69, 1980.
20. Carpenter, R.L. and Van Ummersen, C.A.: The Effects of 2.4 GHz Radiation, J. Microwave Pwr., 3, 3-19, 1968.
21. Clealry, S.: Microwave Cataractogenesis, Proc. I.E.E.E., 68, 49-55, 1980.
22. McCally, R.L., Farrell, R.A., Burgeron, C.B., et. al.: Neuronizing Radiation Damage in the Eye, Johns Hopkins Apl. Tech. Dig., 7, 73-91, 1986.
23. Paz, J.D., Milliken, R., Ingram, W.T.,Arthur, F., and Atkin, A: Potential Ocular Damage from Microwave Exposure During Electrosurgery: Dosimetric Survey, J. Occup. Med., 29, 580-583, 1987.
24. Zimmerman, I.: Dry and Wet Skin Resistance, Cow's Lumbosacral Regions Under 750 KV Lines, Int. J. BioMeteor., 29, 184, 1985.
25. Banks, R.S.: Electric and Magnetic Fields: a New Health Issue, Health and Environ., 2, 1-3, 1988.

11.4

ADVANCED TOPICS IN THE RISK OF BIAS OF THERAPY TRIALS

The Principle of Intention to Treat and Ambiguous Dropouts

Matthias Briel, Victor M. Montori, Pierre Durieux, PJ Devereaux, and Gordon Guyatt

IN THIS CHAPTER

the possible bias introduced by omission of outcome events in patients who discontinued treatment. The investigators could have avoided this problem had they chosen to follow up all patients, irrespective of adherence to treatment.

Clinicians evaluating an RCT need to know whether the researchers followed the intention-to-treat principle. A quick approach is to scan the methods section of the RCT, looking for the phrase "intention-to-treat analysis." Although most RCTs mention this phrase (surely the effect of a campaign about the importance of the intention-to-treat principle), they often misuse it or apply it incorrectly.[8-11] Thus, readers must look not just for this phrase but also for what the trial investigators actually did. In its updated 2010 statement, CONSORT recommends replacing "...*intention-to-treat analysis, a widely misused term*, by a more explicit request for information about retaining participants in their original assigned groups."[12]

PATIENTS WITH LOSS TO FOLLOW-UP

Loss to follow-up leading to missing outcome data in RCTs that report an "intention-to-treat analysis" is common.[8,11] Large loss to follow-up may introduce the same sort of bias as a per-protocol analysis. This is particularly so because patients lost to follow-up tend to have poorer outcomes than patients whom investigators successfully follow up.[13]

Clinicians will find it helpful to separate the issues of intention to treat and loss to follow-up.[14] As we have noted in the previous section, making assumptions about patients lost to follow-up (eg, all had the event of interest or none had the event of interest) and then describing the resulting analysis as an "intention-to-treat analysis" *in no way minimizes the bias that will* occur if the prognosis in those lost to follow-up differs in intervention or control groups or if the magnitude of loss to follow-up differs in the 2 groups.

For instance, Silverstein et al[15] reported the results of an RCT of 8843 patients taking nonsteroidal anti-inflammatory agents for rheumatoid arthritis randomized to receive misoprostol (4404 patients) or placebo (4439 patients) to prevent gastroduodenal complications as judged by outcome assessors masked to treatment allocation. The authors described their analysis as intention to treat. However, they included patients lost to follow-up in the denominator of event rates used for this analysis. Inclusion of these patients in the denominator without inclusion of their outcomes in the numerator assumed that no patient lost to follow-up had gastroduodenal ulcerations. The size of the groups lost (1851 patients in the misoprostol arm and 1617 in the placebo arm) eclipsed the number of patients who experienced the primary end point in each group (25 in the misoprostol group and 42 in the placebo group), leaving the reader uncertain about the true magnitude of the treatment effect. The investigators could have avoided the problem by rigorously following up all patients or, at least, made it controllable by conducting sensitivity analyses with different assumptions for patients lost to follow-up.[16,17]

Investigators should transparently describe how they dealt with loss to follow-up in the analysis section of their reports. Probably the best way of dealing with the situation is to begin by analyzing only those patients for whom one has complete data (called a complete *case analysis*). Investigators should then conduct one or more *sensitivity analyses* using different assumptions for the missing outcomes to assess the robustness of their results. This is true for individual trials and *systematic reviews* and *meta-analyses* of RCTs.[16,17] In the absence of an explicit approach, clinicians should be wary of studies reporting so-called intention-to-treat analyses in the face of substantial loss to follow-up.

CONCLUSIONS

For RCTs to provide unbiased assessments of treatment efficacy, investigators should adhere to the intention-to-treat principle and present analyses in which all patients are included in the groups to which they were randomized. Scanning the methods section for the phrase "intention-to-treat analysis" is insufficient when critically appraising an RCT report. Readers need to check what was actually done in the analysis, with respect to 2 crucial threats to validity: patients who did not follow the protocol and patients lost to follow-up. In unusual situations (toxicity, differential adherence in trials of 2 active treatments, and *noninferiority trials*), an additional per-protocol analysis may provide reassuring (or not so reassuring) information.

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19.1

ADVANCED TOPICS IN DIAGNOSIS

Spectrum Bias

Reem A. Mustafa, Victor M. Montori, Peter Wyer, Thomas B. Newman, Sheri A. Keitz, and Gordon Guyatt

IN THIS CHAPTER

CHOOSING THE WRONG PATIENTS WILL BIAS ESTIMATES OF THE USEFULNESS OF A DIAGNOSTIC TEST

For clinicians to appropriately use diagnostic tests in clinical practice, they need to know how well the tests can distinguish between those who have the *target condition* and those who do not. If investigators choose clinically inappropriate populations for their study of a diagnostic test (introducing what is sometimes called *spectrum bias*), the results may seriously mislead clinicians (see Chapter 18, Diagnostic Tests).

In this chapter, we present a series of examples that expand on the points related to spectrum bias. Working through these examples, you will gain a deeper understanding of which characteristics of a study population are and are not likely to result in misleading results. Readers will find an elaborated version of this demonstration, intended to assist teachers in interactive sessions with small groups, in another publication.[1]

TARGET-POSITIVE PATIENTS WITH UNEQUIVOCALLY SEVERE DISEASE AND TARGET-NEGATIVE PATIENTS WITH NO REASON TO SUSPECT DISEASE ARE THE WRONG PATIENTS TO STUDY

Ideally, the ability of a test to correctly identify patients with a particular disease, condition, or outcome (*target-positive* patients) and those without (*target-negative* patients) would not vary from patient to patient. A test may, however, perform better when used to evaluate patients with more severe disease than it would in patients whose disease is less obvious and/or less advanced. Moreover, clinicians do not need diagnostic tests when the disease is clinically obvious or sufficiently unlikely that they need not seriously consider it.

A study of a diagnostic test involves performing the test of interest, together with a second test or investigation (which we will call the *reference standard*, *criterion standard*, or *gold standard*) in patients with and without the disease or condition of interest. We accept the results of the reference standard as the criterion by which the results of the test under investigation are assessed.

In designing such a study, investigators sometimes choose patients with unequivocally far-advanced disease together with unequivocally disease-free people, such as healthy asymptomatic volunteers. This approach ensures that the criterion standard will not misclassify any patients and may be appropriate in the early stages of developing a test. Any study performed on a population that lacks diagnostic uncertainty may, however, produce a biased estimate of a test's performance relative to a study restricted to patients for whom the test would be clinically indicated.

DISTRIBUTIONS OF TEST RESULTS ILLUSTRATE THE SPECTRUM PROBLEM

A crucial issue in the design of a diagnostic-test study is the distribution of severity of illness or abnormality among the patients who were enrolled. We refer to this distribution as the spectrum of disease, illness, or abnormality.

For example, consider brain natriuretic peptide (BNP), which is a hormone that the ventricles of the heart secrete in response to expansion. Plasma levels of BNP increase in congestive heart failure (CHF). Consequently, investigators have suggested BNP as a test to distinguish between CHF and other causes of acute dyspnea among patients presenting to emergency departments.[2]

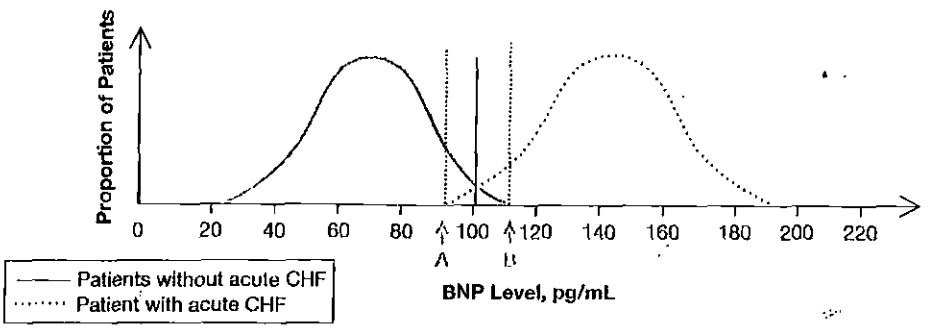
One study reported promising results using a BNP cutoff of 100 pg/mL.[3,4] In thinking about the use of BNP as a test for CHF among patients with acute dyspnea, consider Figure 19.1-1. The horizontal axis corresponds to increasing values of BNP. The 2 bell curves constitute hypothetical probability density plots of the distribution of BNP values among patients with and without CHF. The height of the vertical axis at any point in either curve reflects the proportion of emergency department patients having the corresponding BNP result. Aside from the choice of cutoff value, this figure is a hypothetical illustration that does not directly reflect the results of any actual study.

The bell curve on the left of Figure 19.1-1 represents a schematic of the distribution of BNP values in a group of young individuals with known asthma and no risk factors for CHF. They will tend to have very low levels of circulating BNP. The bell curve on the right represents the distribution of BNP values in older patients with unequivocal and severe acute CHF. Such patients will have test results clustered on the high end of the scale.

If Figure 19.1-1 accurately represented the performance of BNP in distinguishing between patients with and without CHF as the cause of their symptoms, BNP would be a very good test: the 2 curves demonstrate very little overlap. For BNP values above

FIGURE 19.1-1

Distribution of Brain Natriuretic Peptide Values Among Patients With and Without Congestive Heart Failure: Patients With Asthma and Those With Severe Heart Failure



The height of the bell curve at each point reflects the proportion of the patient subgroup having the corresponding BNP value. Patients without CHF (left hand curve) are made up of younger patients with known asthma and no risk factors for CHF. The patients with CHF are older and are clinically severe and unequivocal. Treating clinicians in the emergency department have little uncertainty regarding the cause of dyspnea in any of these patients. Abbreviations: BNP, brain natriuretic peptide; CHF, congestive heart failure.

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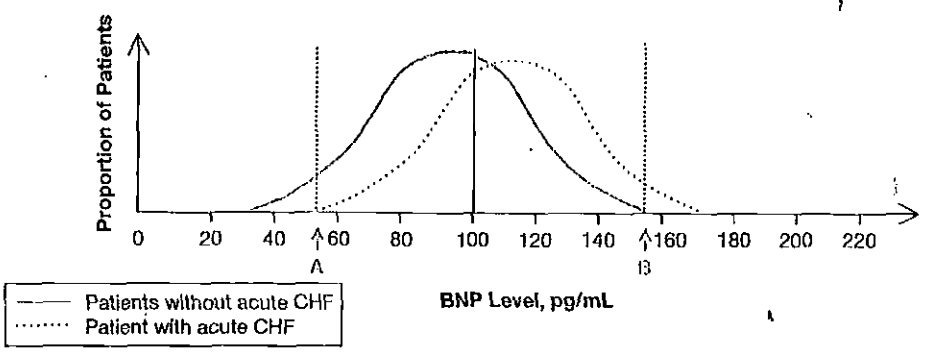
FIGURE 19.1-2

Distribution of Brain Natriuretic Peptide Values Among Patients With and Without Congestive Heart Failure



Individuals had a history of CHF and asthma with or without CHF. The probability density distributions now reflect a study population of middle-aged patients who all have recurrent asthma and chronic CHF. The patients whose dyspnea is due to asthma exacerbations manifest test results similar to those whose symptoms are being caused by acute CHF. Abbreviations: BNP, brain natriuretic peptide; CHF, congestive heart failure.

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22

The Process of a Systematic Review and Meta-analysis

M. Hassan Murad, Roman Jaeschke, PJ Devereaux, Kameshwar Prasad, Alonso Carrasco-Labra, Thomas Agoritsas, Deborah J. Cook, and Gordon Guyatt

IN THIS CHAPTER

management), have no explicit criteria for selecting the included studies, do not include systematic assessments of the *risk of bias* associated with *primary studies*, and do not provide quantitative best estimates or rate the confidence in these estimates. The traditional narrative review articles are useful for obtaining a broad overview of a clinical condition but may not provide a reliable and unbiased answer to a focused clinical question.

Why Seek Systematic Reviews?

When searching for evidence to answer a clinical question, it is preferable to seek a systematic review, especially one that includes a meta-analysis, rather than looking for the best individual study or studies. The reasons include the following:

1. Single studies are liable to be unrepresentative of the total body of evidence, and their results may therefore be misleading.
2. Collecting and appraising a number of studies take time you probably do not have.
3. A systematic review is often accompanied by a meta-analysis to provide the best estimate of effect that increases precision and facilitates clinical decision making.
4. If the systematic review is performed well, it will likely provide all of the relevant evidence with an assessment of the best estimates of effect and the confidence they warrant.
5. Systematic reviews include a greater range of patients than any single study, potentially enhancing your confidence in applying the results to the patient before you.

A Synopsis of the Process of a Systematic Review and Meta-analysis

In applying the *Users' Guides*, you will find it useful to have a clear understanding of the process of conducting a systematic review and meta-analysis. Figure 22-2 shows how the process begins with the definition of the question, which is synonymous with specifying eligibility criteria for deciding which studies to include in a review. These criteria define the population, the exposures or interventions, and the outcomes of interest. A systematic review also may restrict studies to those that minimize the risk of bias. For example, systematic reviews that address a question of therapy often will include only RCTs.

FIGURE 22-1

The Overlap of Study Designs: Systematic Review and Meta-analysis

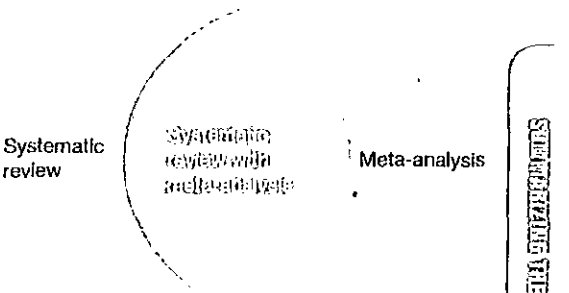
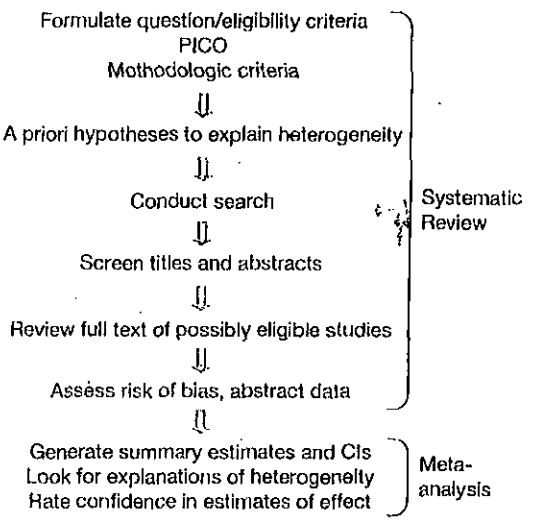


FIGURE 22-2

The Process of Conducting a Systematic Review and Meta-analysis



In a systematic review without meta-analysis, the step of generating summary estimates and confidence intervals is not applicable. If the systematic review includes a meta-analysis and presents estimates of effect from individual studies, seeking explanation for heterogeneity and rating confidence in estimates is possible.

Abbreviations: CI, confidence interval; PICO, Patient, Intervention, Comparison, Outcome.

Having specified their selection criteria, reviewers will conduct a comprehensive search of the literature in all relevant medical databases, which typically yields a large number of potentially relevant titles and abstracts. They then apply the selection criteria to the titles and abstracts, arriving at a smaller number of articles that they retrieve. Once again, the reviewers apply the selection criteria, this time to the complete reports.

Having completed the culling process, the reviewers assess the risk of bias of the individual studies and abstract data from each study. Finally, they summarize the results, including, if appropriate, a quantitative synthesis or meta-analysis. The meta-analysis provides *pooled estimates* (ie, combined estimates) of the effect on each of the outcomes of interest, along with the associated CIs. Meta-analyses frequently include an examination of the differences in effect estimates across included studies in an attempt to explain differences in results (exploring *heterogeneity*). If based on previously specified hypotheses about possible differences in patients, interventions, or outcomes that may explain differences in results, such explorations become more credible (see Chapter 25.2, How to Use a Subgroup Analysis).

BOX 22-1

Users' Guides for Credibility of the Systematic Review Process

Did the review explicitly address a sensible clinical question?

Was the search for relevant studies exhaustive?

Was the risk of bias of the primary studies assessed?

Did the review address possible explanations of between-study differences in results?

Did the review present results that are ready for clinical application?

Were selection and assessments of studies reproducible?

Did the review address confidence in effect estimates?

Judging the Credibility of the Effect Estimates

When applying the results of a systematic review to patient care, you can look for estimates of effect. A systematic review without a meta-analysis typically presents results from individual studies; the meta-analysis adds a single pooled (combined) estimate of effect, with an associated CI, for each relevant outcome. Pooled estimates could be for therapy outcomes (eg, death, myocardial infarction, quality of life, late catastrophic adverse effects), estimates of the properties of diagnostic tests (eg, *likelihood ratios*), or estimates of patients' likely outcomes (eg, prognosis). Clinicians need to know the extent to which they can trust these estimates.

Two fundamental problems can undermine this trust. One is the extent to which systematic review authors have applied rigorous methods in conducting their review. We refer to this as the *credibility* of the review.[3] By credibility, we mean the extent to which the design and conduct of the review are likely to have protected against misleading results.[4] As you will see, credibility may be undermined by eligibility criteria that are inappropriate or not specified, the conduct of an inadequate search, and the omission of risk of bias assessments of individual studies (see Box 22-1 for issues to be considered in the credibility of the review process; these issues are applicable to any systematic review, with or without a meta-analysis).

A highly credible review—one that has adhered to methodologic standards—may nevertheless leave us with only very low confidence in estimates of effect. Common reasons for this include the following: the individual studies may be plagued by high risk of bias and inconsistent results, even the pooled (combined) sample sizes may be small and the results may be imprecise, and the patients enrolled in the studies may differ in important ways from those in whom we are interested. This chapter deals with credibility assessment of the review process; the next chapter (Chapter 23, Understanding and Applying the Results of a Systematic Review and Meta-analysis) will guide you in deciding how much confidence we can place on estimates of effect in the presence of a credible review process.

Was the Search for Relevant Studies Detailed and Exhaustive?

Systematic reviews are at risk of presenting misleading results if they fail to secure a complete, or at least representative, sample of the available eligible studies. To achieve this objective, reviewers search bibliographic databases. For most clinical questions, searching a single database is insufficient and can lead to missing important studies. Therefore, searching MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials is recommended for most clinical questions.[7] Searching other databases may be required, depending on the nature of the review question. The systematic review authors check the reference lists of the articles they retrieve and seek personal contact with experts in the area. It also may be important to examine recently published abstracts presented at scientific meetings and to look at less frequently used databases, including those that summarize doctoral theses and databases of ongoing trials held by pharmaceutical companies or databases of ongoing registered trials.

Another important source of unpublished studies is the US Food and Drug Administration (FDA) reviews of new drug applications. A study that evaluated the risk of dyspepsia associated with the use of nonsteroidal anti-inflammatory drugs found that searching FDA records yielded 11 trials, of which only 1 was published.[8] Another study of FDA reports found that they included numerous unpublished studies, and the findings of these studies can appreciably alter the estimates of effect.[9] Unless the authors of systematic reviews tell us what they did to locate the studies, it is difficult to know how likely it is that relevant studies were missed.

Reporting bias occurs in a number of forms, the most familiar of which is the failure to report or publish studies with negative results. This *publication bias* may result in misleading results of systematic reviews that fail to include unpublished studies.[10,11]

If authors include unpublished studies in a review, they should try to obtain full reports, and they should use the same criteria to appraise the risk of bias of both published and unpublished studies. There is a variety of techniques available to explore the possibility of publication bias, but none of them are fully satisfactory. Systematic reviews based on a small number of studies with limited total sample sizes are particularly susceptible to publication bias, especially if most or all of the studies have been sponsored by a commercial entity with a vested interest in the results.

Another increasingly recognized form of reporting bias occurs when investigators measure a number of outcomes but report only those that favor the *experimental intervention* or those that favor the intervention most strongly (*selective outcome reporting bias*). If reviewers report that they have successfully contacted authors of primary studies and were assured of the full disclosure of results, concern about reporting bias decreases.

Reviewers may go even farther than simply contacting the authors of primary studies. They may recruit these investigators as collaborators in their review, and in the process, they may obtain individual patient records. Such *individual patient data meta-analysis* can facilitate powerful analyses (addressing issues such as true *intention-to-treat* analyses and informed *subgroup analyses*), which may strengthen the inferences from a systematic review.

Was the Risk of Bias of the Primary Studies Assessed?

Even if a systematic review includes only RCTs, knowing the extent to which each individual trial used safeguards against bias is important. Differences in study methods might explain important differences among the results.[12] For example, less rigorous studies sometimes overestimate the effectiveness of therapeutic and preventive interventions.[13] Even if the results of different studies are consistent, determining their risk of bias is still important. Consistent results are less compelling if they come from studies with a high risk of bias than if they come from studies with a low risk of bias.

Consistent results from *observational studies* putatively addressing treatment issues also should raise concern. Clinicians may systematically select patients with a good prognosis to receive therapy, and this pattern of practice may be consistent over time and geographic setting. There are many

DIFFERENTIATION OF IEI

IEI cases with EMF attributed symptoms needs to be differentiated from other IEI cases:

a) there should be a search for a symptom cluster: Present studies were very valuable in determining groups of self-declared EHS cases. There is a need not to restrict the attempt to self-declared EHS cases but to study the group of IEI on a broader scale, e.g. by hypothesis-based studies of symptom groups according to the frequency of occurrence or symptom-trigger by specific sources.

b) there is a need to define IEI inclusion/exclusion criteria, e.g. definitions based on baseline tests for characterizing the status of the autonomic nervous system and the psychological/ psychiatric status.

PROVOCATION STUDIES

Provocation studies are considered to be the most powerful way of studying/ proving a causal relationship. For proper design, apart from ethical considerations, the following aspects need to be considered:

- differentiation between potential electromagnetic versus psychological/ psychophysiological impact by adequate tests
- double-blind placebo-controlled crossover design
- inclusion of an appropriate psychiatric control group exhibiting similar symptoms (e.g. anxiety, affective disorders, somatoform reactions, etc.)
- inclusion of a positive control factor, e.g. other environmental stressors like sound, flickering light or mental stress
- accounting for potentially different individual reaction onset/recovery time constants
- characterization of provocation conditions, including the duration of exposure and the duration of washout times
- measurement of the EMF background level (which should be well below the provocation level)
- consideration of person's belief/ experience when choosing provocation factors (e.g. fields, exposure time)

- use of well documented and validated questionnaires and test procedures with preference given to yes/no questions (such as the Minnesota MMPI-2 test protocol or the SCL-90R- symptom checklist)
- neuropsychological testing before and after exposure
- consideration of appropriate signal characteristics, e.g. frequency, modulation and intensity

There is a need to harmonize protocols and establish multinational/ international cooperation.

EPIDEMIOLOGICAL STUDIES

For the time being, epidemiological studies are not considered helpful. The reasons for this are the following:

- the definition of "cases" is still lacking
- possible device-specific reactions could be missed because of the different devices encountered in daily life
- exposure level might not necessarily be a selection criterion for exposure groups

(iii) Report on policy options, communications with IEI individuals and recommendations to national authorities

Rapporteur: Jill Meara, National Radiological Protection Board, United Kingdom
Participants: Pavel Sistek, National Reference Laboratory on Non-Ionizing EMF, Czech Republic
Wendla Paile, STUK - Radiation and Nuclear Safety Authority, Finland
Fabriziomaria Gobba, University of Modena & Reggio Emilia, Italy
Christopher Muller, ergonomie & technologie (e&t) GmbH, Switzerland
Emilie van Deventer, World Health Organization, Switzerland

INFORMATION FOR GENERAL PUBLIC

WHO to develop a general fact sheet that includes the following points:

- range of symptoms of IEI
- no attribution of causality to EMF
- do not include prevalence of EHS but rather prevalence of the different symptoms (and longstanding history of these) in general population

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Education

Research Masters Fellowship in Biomedical Informatics. Columbia University.	2000-2003
Internship and Residency, General Internal Medicine. Mayo Clinic.	1997-2000
Medical Doctor. University of Nevada.	1993-1997
BS, Electrical Engineering. Kettering University.	1984-1989

Experience

Cerner, Malvern Pennsylvania 2015-present

- **Clinical Consultant, HS Innovations Center**
  - ✓ Responsible for Content Process Alignment

Siemens Medical Solutions, Malvern, Pennsylvania 2004-2015

- **Physician Consultant, Subject Matter Expert**
  - ✓ Guided implementation of the first live clinical uses of the workflow engine.
  - ✓ Informatics and Domain expertise in the development of a multi entity EMR with Inpatient CPOE and clinical documentation.
  - ✓ Designed and implemented patented order search algorithm.
  - ✓ Co-chair for IHE Patient Care Coordination Planning Committee.
  - ✓ Co-chair for IHE Patient Care Coordination Technical Committee.
  - ✓ Co-chair for HL7 Patient Care Technical Committee.
  - ✓ Co-editor for HL7 CCD.
  - ✓ Project lead and scenario designer for HIMSS Interoperability Showcase 2006, 2007, 2008. (at the time the largest demonstration of system clinical information system interoperability in the world)
  - ✓ Key expert for Physician Documentation
  - ✓ Key expert for Hospital to Ambulatory Interoperability
  - ✓ Key expert in Sales events to Physicians
  - ✓ Key expert in Clinical Architecture
  - ✓ Industry voice and thought leadership in area of Interoperability, Clinical workflow, and Meaningful use.
  - ✓ Certification Officer – Coordinated successful CCHIT and ONC/ATCB Certification of 3 clinical solutions.
  - ✓ Product Owner for Soarian Clincials Content
  - ✓ Responsible for Siemens HS Overall Clinical Content Strategy

Great Valley Health, Bryn Mawr, Pennsylvania 2003-present

- **Hospitalist Physician – Internal Medicine**
  - ✓ Direct patient care. Actively practice medicine.
  - ✓ Physician Council for IT oversight

Columbia University, New York, New York 2000-2003

- **Assistant Attending / Instructor of Clinical Medicine.**
  - ✓ Direct patient care. Resident supervision.
- **NLM Research Masters Fellow.**
  - ✓ Developed an integrated, patient centered, role based, asynchronous messaging system that is accessible from standard browsers and palm devices.
  - ✓ Participated in development of a wireless, handheld version of Columbia's Clinical Information System known as PalmCIS. Contributions ranged from providing clinical expertise to writing driver code.
  - ✓ Published on the relationship between information needs, communication failures and adverse events. Paper nominated for the Diane Forsythe Award at the AMIA 2001 Fall Symposium.
  - ✓ Presented and taught tutorials on the use of a variety of machine learning techniques (Support Vector Machines, decision-trees, Naive-Bayes, etc) for data mining free text narratives.
  - ✓ Developed heuristic and machine learning approaches to automatically identify conclusion sentences in medical abstracts for the National Library of Medicine.

Mayo Clinic, Rochester, MN 1997-2000

- **Resident, General Internal Medicine.**
  - ✓ Conducted formal usability studies of a clinical problem list manager. Paper nominated for best paper at the AMIA 1999 Fall Symposium.
  - ✓ Member of IDX Orders Implementation group, the group for the improvement of the Electronic Results Inquiry System (ERIS), and the committee to oversee the development of hospital based computer applications.

University of Nevada, School of Medicine, Reno, NV 1993-1997

- **Medical Student / Research Assistant**
  - ✓ Developed a novel approach to discovering iterations between model attributes in datasets using a genetic algorithm and Neural Networks.

General Motors, Chevrolet-Pontiac-Canada Group, Van Nuys, CA 1984-1992

- **Process Engineer.**
  - ✓ Responsible for paint mixing, delivery, electrostatic undercoat, and computer controlled painting systems for 1 shift (approximate production 50,000 cars per year).
  - ✓ Implemented a real time paint flow tracking system. One of the first systems of its kind using fiber optic transducers, and closed loop feedback. Similar systems are now used at several GM Assembly plants in part due to success of this system.
  - ✓ Supervised 15 tradesmen.
  - ✓ Evaluated the impact of parallel paint lines on paint quality and downstream scheduling for a General Motors Assembly Plant. Results demonstrated million dollar cost savings associated with just-in-time materials management.

Publications

Peer Reviewed Conference Proceedings:

1. Mendonca EA, Chen ES, Stetson PD, McKnight LK, Lei J, Cimino JJ. Approach to mobile information and communication for health care. Int J Med Inform. 2004 Aug;73(7-8):631-8.
2. Chen ES, Mendonca EA, McKnight LK, Stetson PD, Lei J, Cimino JJ. PalmCIS: a wireless handheld application for satisfying clinician information needs. J Am Med Inform Assoc 2004 Jan-Feb;11(1):19-28.
3. LK McKnight, Srinivasan P. Categorization of Sentence Types in Medical Abstracts. AMIA Annual Symposium, 2003. pp.440-4.
4. Cimino JJ, Chen ES, McKnight LK, Stetson PD, Lei J, Mendonca EA. Mobile information and coordination for healthcare. In: Marin HF, Marques EP, Hovenga E, Goossen W, edts. NI 2003 Proceedings 8th International Congress in Nursing Informatics - e-Health for all: designing nursing agenda for the future. Rio de Janeiro, RJ, Brazil:285-9.
5. LK McKnight, A Wilcox, G Hripcsak. The Effect of Sample Size and Disease Prevalence on Supervised Machine Learning of Narrative Data. Proceedings, AMIA Annual Symposium, 2002. 519-22.
6. LK McKnight, PD Stetson, S Bakken, C Curran, JJ Cimino. Perceived Information Needs and Communication Difficulties of Inpatient Physicians and Nurses. Proceedings, AMIA Annual Symposium, 2001. pp.453-8. Republished in JAMIA 2002(9):6 S64-9.
7. PD Stetson, LK McKnight, S Bakken, C Curran, TT Kubose, JJ Cimino. Development of an Ontology to Model Medical Errors, Information Needs, and the Clinical Communication Space. Proceedings, AMIA Annual Symposium, 2001. pp.672-7.
8. LK McKnight, PL Elkin, PV Ogren, CG Chute. BARRIERS TO THE CLINICAL IMPLEMENTATION OF COMPOSITIONALITY: A Usability Study of YATN. Proceedings, AMIA Annual Symposium. 1999. pp.320-4.

Abstracts:

1. LK McKnight, PD Stetson, ES Chen, JJ Cimino. Improving Clinical Communication with a Virtual Whiteboard. Proceedings, AMIA Annual Symposium, 2002. p.1102.
2. PD Stetson, LK McKnight, ES Chen, JJ Cimino. Design of a Web-Based Care Team Scheduler for PalmCIS. Proceedings, AMIA Annual Symposium, 2002. p1172.
3. ES Chen, LK McKnight, PD Stetson, JJ Cimino. Issues in Developing Clinical Applications for the Wireless Environment. Proceedings, AMIA Annual Symposium, 2002. p.995.
4. LK McKnight, PH Goodman. APPLYING THE PRINCIPLES OF NATURAL SELECTION TO STATISTICAL ANALYSIS: Using a genetic algorithm to discover important interactions among clinical predictors of death. Journal of Investigational Medicine. 1995. p.184A.

Other Talks and Presentations:

1. A primer on Support Vector Machines. Departmental Conference, 12/2002.
2. Perl as a Component Model. Advanced Software Engineering Course, 12/2002.
3. Introduction to Unsupervised Learning. Methods in Medical Informatics Course, 4/2002.
4. Introduction to Supervised Learning. Methods in Medical Informatics Course, 4/2002.
5. Patients and the Internet. Internal Medicine Division Conference, 2/2002.
6. A Financial Analysis of PalmCIS. Economics of Medical Informatics Course, 12/2001.

Undergraduate Thesis:

1. LK McKnight. Vehicle Sequencing for Open Paint Systems. GMI Press, 1989.

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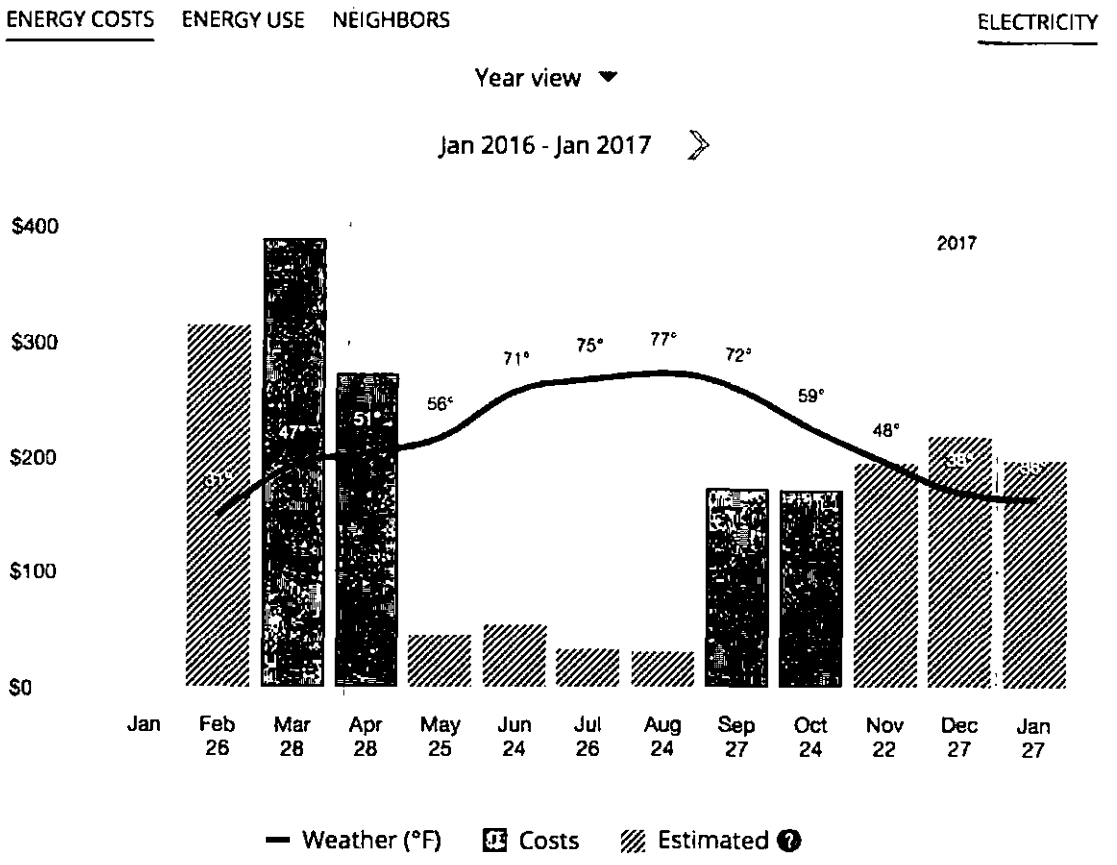
C-2017-2621057
4/10/18 Phila 32

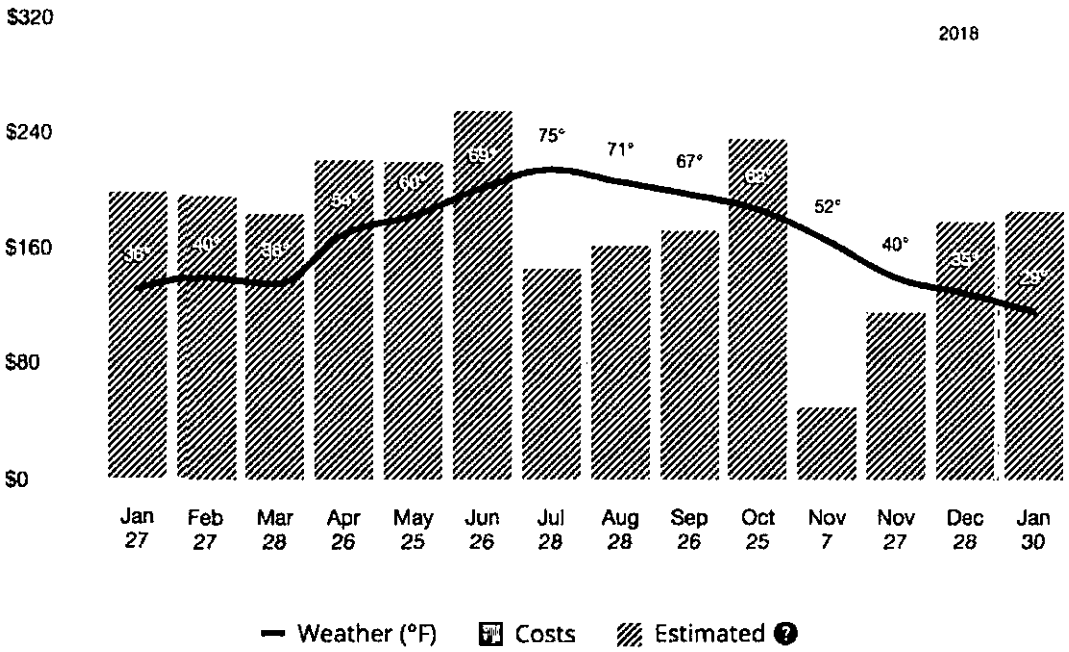
Online bills of when 'estimated'



ENERGY COSTS ENERGY USE NEIGHBORS ELECTRICITY

Year view

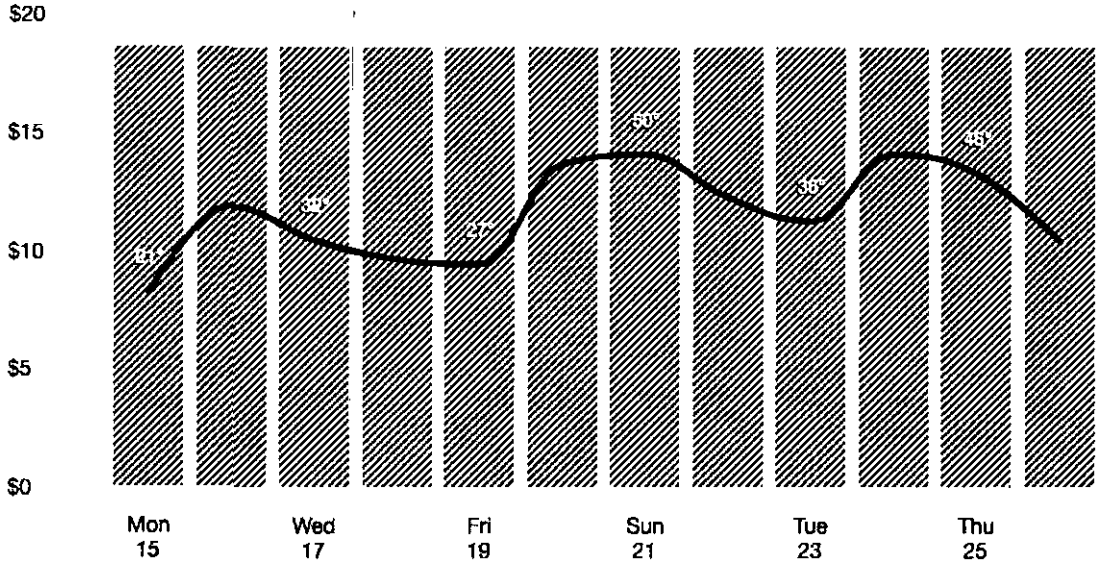
Jan 2017 - Jan 2018



ENERGY COSTS ENERGY USE NEIGHBORS ELECTRICITY

Bill view

Feb 9, 2016 - Feb 26, 2016



— Weather (°F) Costs Estimated

ENERGY COSTS ENERGY USE NEIGHBORS ELECTRICITY

Bill view

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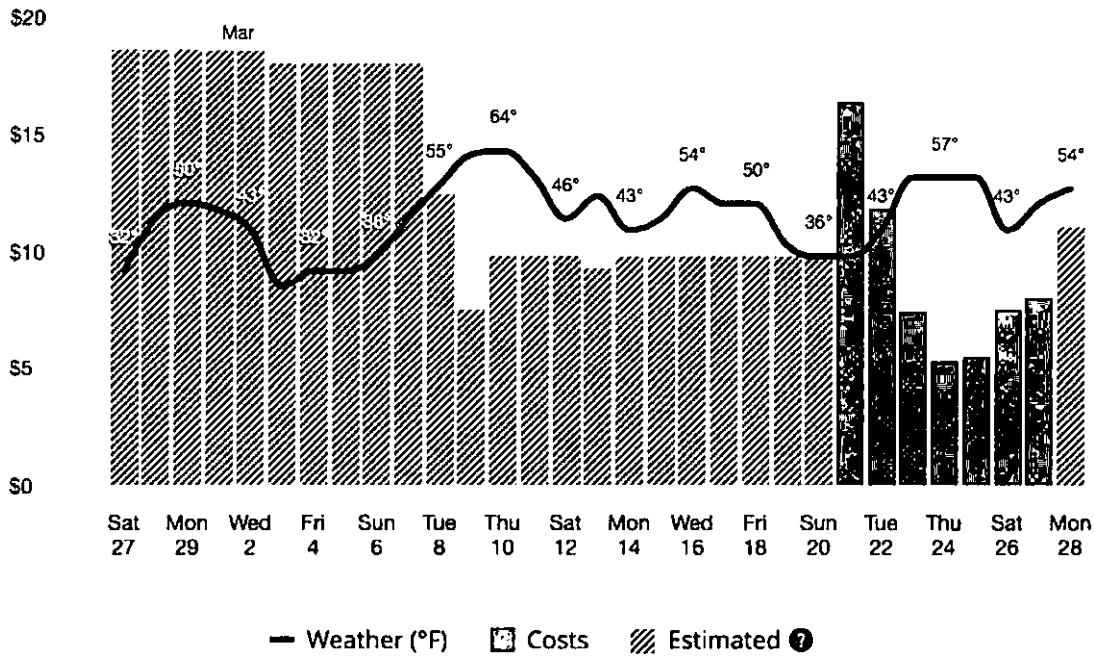

ENERGY COSTS ENERGY USE NEIGHBORS ELECTRICITY

Bill view

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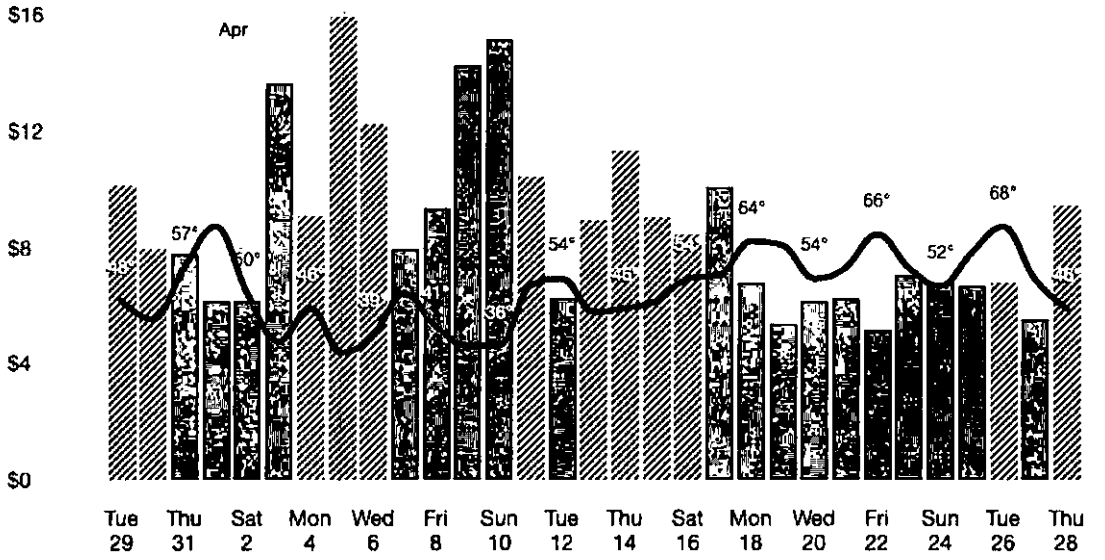

ENERGY COSTS ENERGY USE NEIGHBORS ELECTRICITY

Bill view

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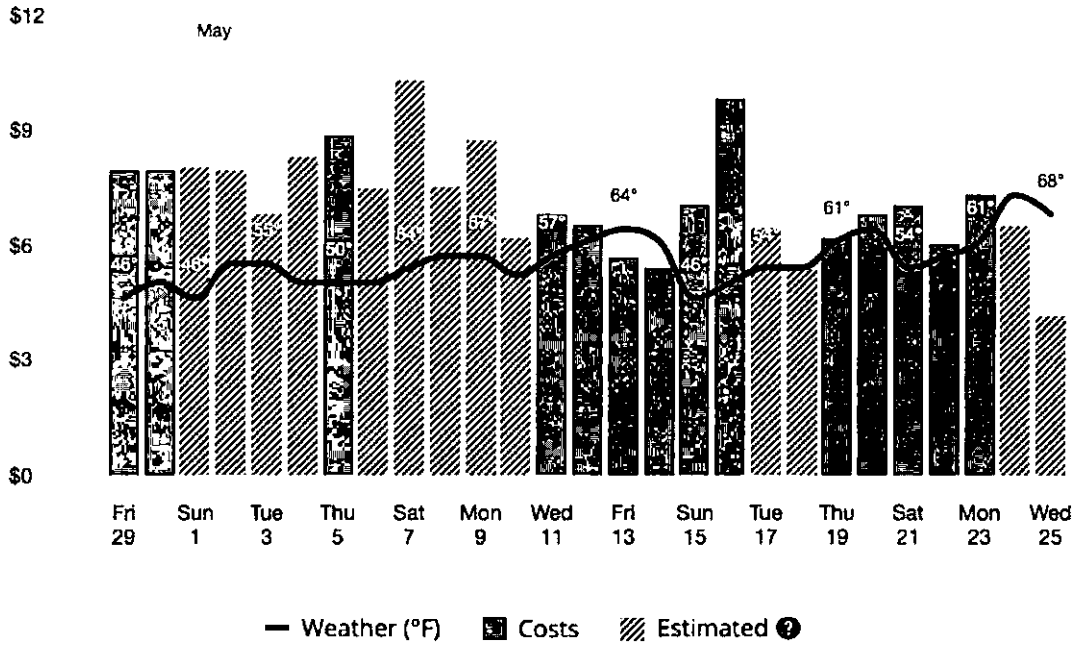

ENERGY COSTS ENERGY USE NEIGHBORS ELECTRICITY

Bill view

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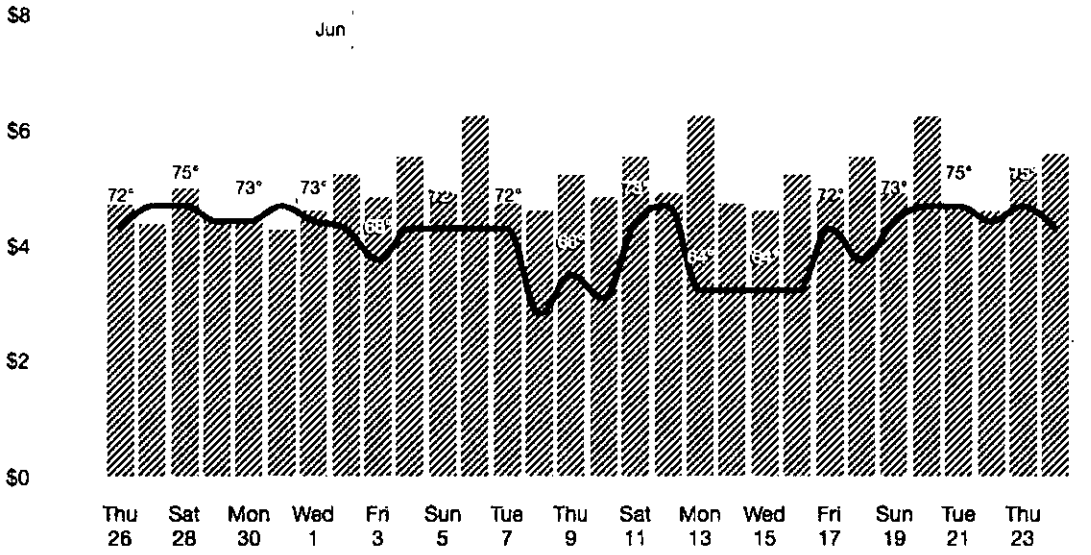

ENERGY COSTS ENERGY USE NEIGHBORS ELECTRICITY

Bill view

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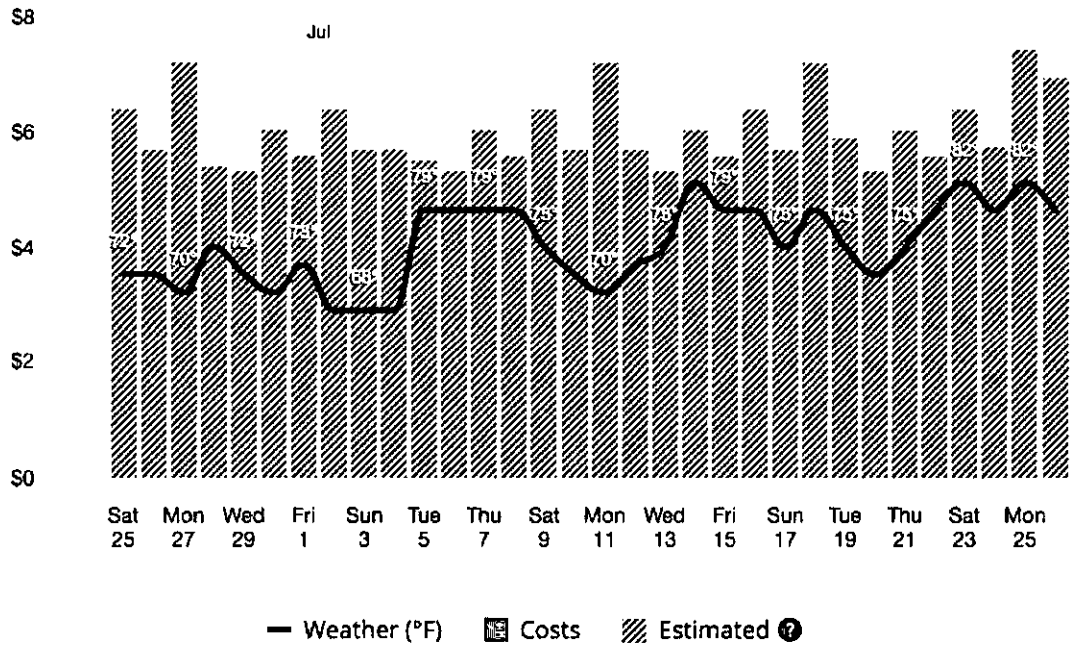

ENERGY COSTS ENERGY USE NEIGHBORS ELECTRICITY

Bill view

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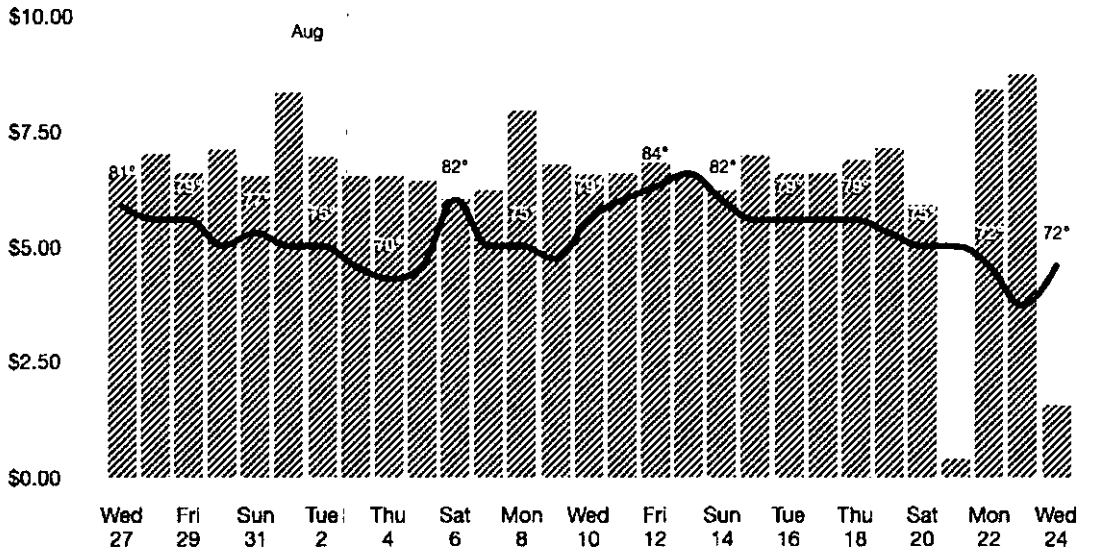
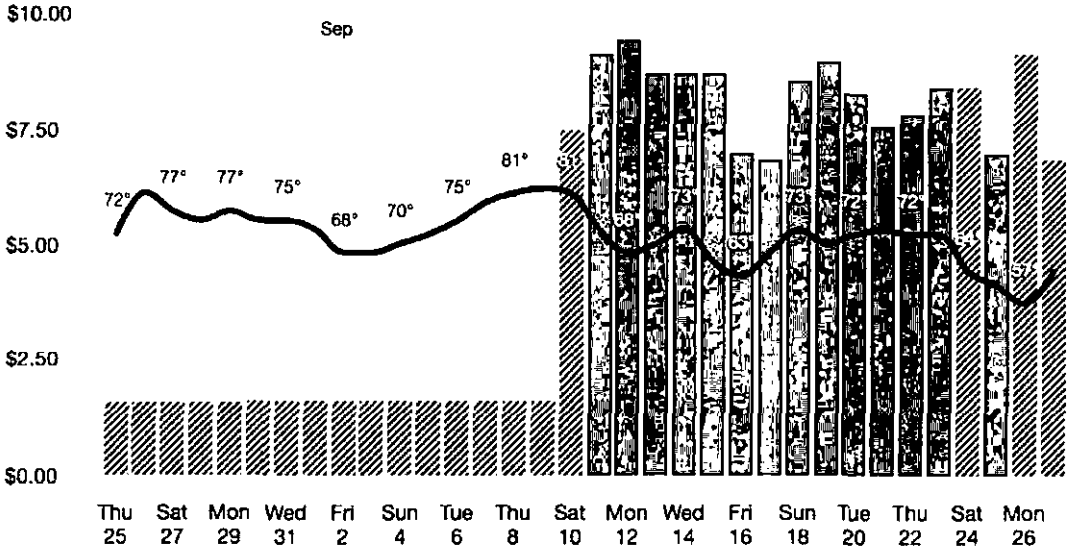


Weather (°F) Costs Estimated

ENERGY COSTS ENERGY USE NEIGHBORS ELECTRICITY

Bill view

Aug 25, 2016 - Sep 27, 2016



ENERGY COSTS ENERGY USE NEIGHBORS ELECTRICITY

Bill view

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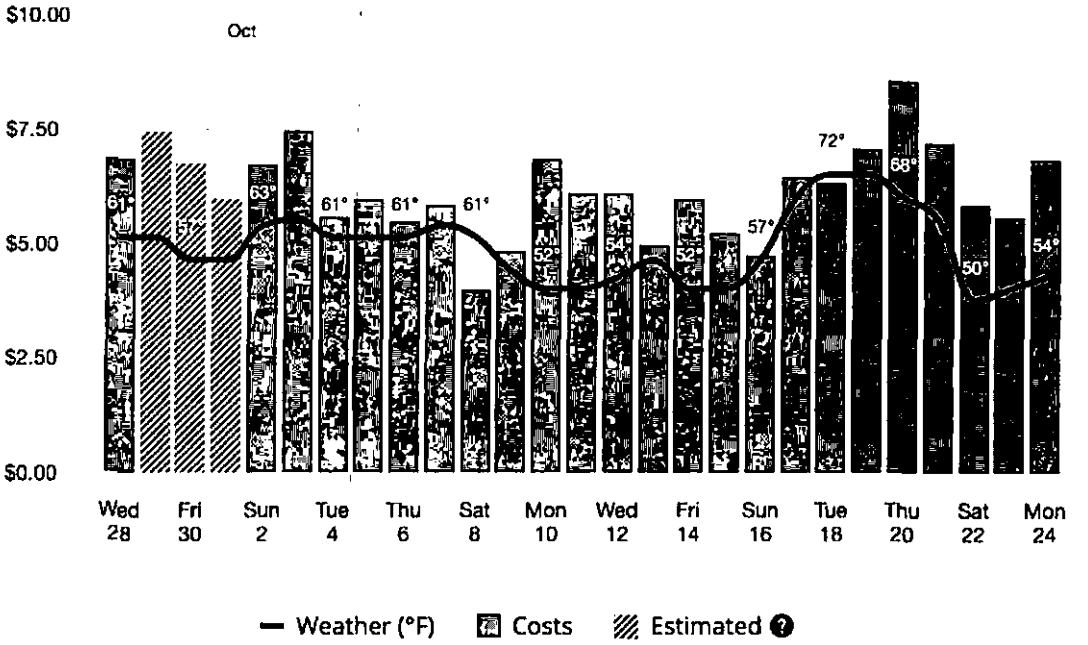

ENERGY COSTS ENERGY USE NEIGHBORS ELECTRICITY

Bill view

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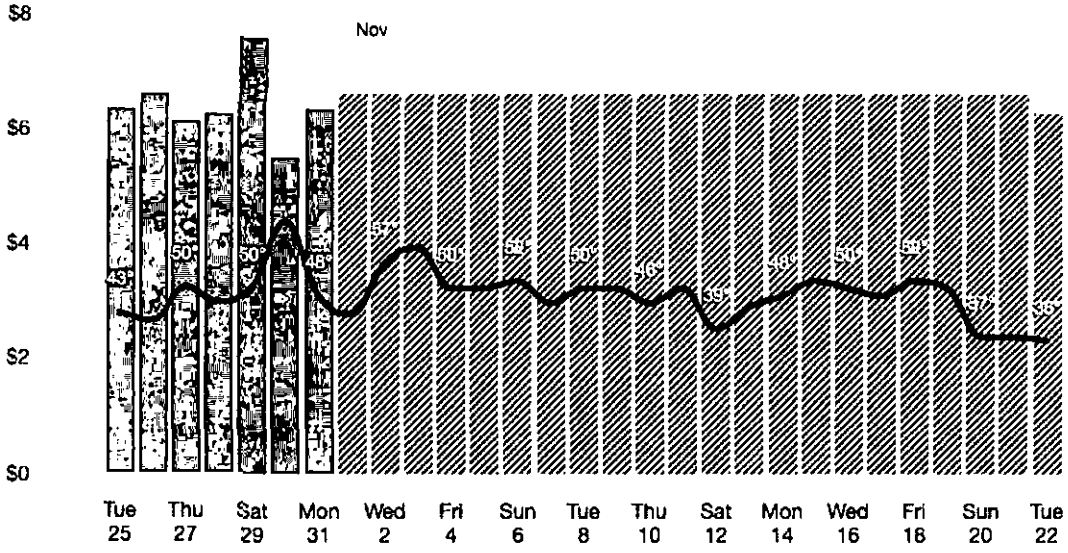

ENERGY COSTS ENERGY USE NEIGHBORS ELECTRICITY

Bill view

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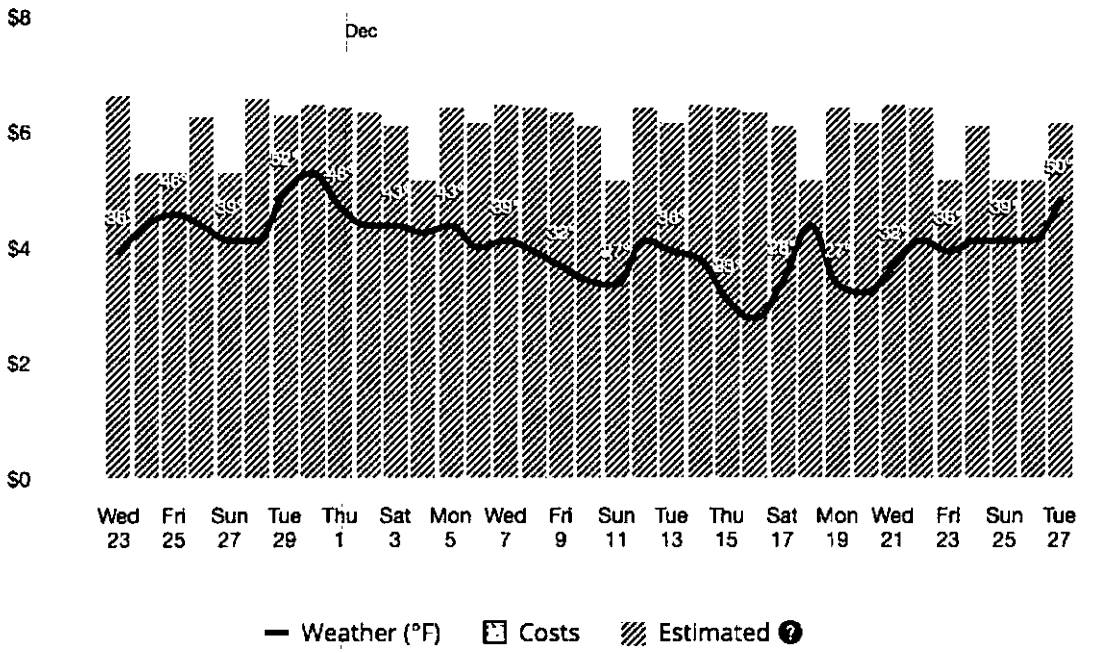

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Name: LAWRENCE MCKNIGHT
Account Number: 89900-01209
Phone Number: 610-459-1031
Service Address: 258 HEYBURN RD, CHADDS FORD

Billing Summary

Bill Date	09/26/2016
Thank you for your payment of $227.92	
Thank you for your payment of $261.02	
Thank you for your payment of $236.14	
Thank you for your payment of $200.60	
Thank you for your payment of $273.80	
Estimated bill	$-116.12
Estimated bill	$-120.02
Total Other Charges	**$-236.14**
Current Period Charges	
Electric	$165.92
Total New Charges	**$165.92**
Total Amount Due on 10/18/2016	**$0.00**

Your remaining excess credit is $759.76

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C-2017-2621057
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Phila.

General Information

Next scheduled meter reading: **October 26, 2016**
PECO, 2301 Market Street, Philadelphia, PA 19103-1380. If you have any questions or concerns, please call **1-800-494-4000** before the due date. Si tiene alguna pregunta, favor de llamar al numero **1-800-494-4000** antes de la fecha de vencimiento.

Customer Self Service - Manage Your Account 24/7
- www.peco.com/ebill - Go paperless: receive and pay your bill
- www.peco.com/service - Start, stop and transfer your service
- www.peco.com/Smartideas - Save energy and money
- Pay by phone with credit/debit card at 1-877-432-9384 ($2.35 fee)

Contact Your Electric Supplier:
Think Energy, P.O. Box 27004, Lehigh Valley, PA 18002, 865-252-0078

Message Center

From PECO:

Estimated Meter Reading.

Corrected Bill

New charges contain estimated total state taxes of $9.02, including $9.79 for State Gross Receipts Tax.

Your estimated electric price to compare is $0.0778 per kWh. This may change in March, June, September and December. For more information and supplier offers visit www.PAPowerSwitch.com and www.oca.state.pa.us.

Your Total Account Balance of $-759.76 includes your Total Amount Due and all other Arrangement/Agreement balances that are on this account.

Credit balance on this bill will be applied to your next standard bill.

This bill for electric service covers an extended period of time. Our normal bill period is 28 to 35 days.

When paying in person, please bring the entire bill

(continued on next page)

Return only this portion with your check made payable to PECO. Please write your account number on your check.

PECO An Exelon Company

☐ **Check here to enroll in Power Pay automatic account debit and complete form on reverse side.**

☐ **Check here to pledge a donation to MEAF and complete form on reverse side.**

To pay by phone call 1-877-432-9384. A convenience fee will apply.

LAWRENCE MCKNIGHT
258 HEYBURN RD
CHADDS FORD, PA 19317-9782

Account Number
89900-01209

Payment Receipt Stamp

Payment Amount

Please pay this amount by 10/18/2016 **$0.00**

PECO - PAYMENT PROCESSING
PO BOX 37629
PHILADELPHIA PA 19101-0629

899000120900000000062920000009