Chapter 8

Ethical Issues in Headache Research and Management

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Medical research is the means to a better understanding of the etiologic and pathogenetic mechanisms of human disease. These in turn are essential to progress in classification, diagnosis, treatment, and prevention. Headache research can, ultimately, be performed only in humans: the peculiarly symptomatic nature of headache syndromes—pain, nausea, hyperesthesia, debility—and the changes that occur with therapy require subjective description and cognitive interpretation. Headache research, whether on patients or volunteers, is strongly conditioned by good research ethics. It shares a number of fundamental ethical demands with other biomedical studies having humans as subjects, but also presents various special demands (35).

ETHICAL PRINCIPLES

Practical ethics are concerned much less with the idea that final solutions to ethical problems exist as truths than with the perception of tensions, to be resolved by applying generally accepted principles. A number of ethical principles are established in medical practice and declared in guidelines. They include autonomy of patients; justice, with particular reference to resource allocation in a context of limited resources (distributive justice); nonmaleficence and beneficence (3); and the medical professional ethical principles of veracity (truth telling) (45), fidelity (the keeping of promises), and confidentiality. However, recent challenges to the view that the approach to medical ethics should be on the basis of such a set of ethical principles (*"principlism"*) (3) favor a more general recognition of the needs of patients, the responsibilities of doctors, the good of society as a whole, and deserts.

Needs of patients is not the same as the *needs of the patient*. Participation as a subject in clinical research is not always (in fact, not usually) in the direct interests of the subject. In such circumstances, ethical justification of clinical research depends on its serving the good of society as a whole. This more general approach to determining what is ethical creates a more comfortable climate in which to propose clinical research (35), and is apparent in long-established ethical doctrine. The Declaration of Helsinki (67) enjoins physicians that "The health of my patient will be my first consideration"; but it opens with: "It is the duty of the physician to safeguard the health of *the people*" (emphasis added). Similar introductions are found in newer international codes (8–11).

ISSUES IN HEADACHE RESEARCH

Ethical research involving humans, even when serving the good of society as a whole, has other necessary features. Independent research ethics committees look to and consider these in the light of accepted generic or specific guidelines on research ethics:

1. originality of the idea and methodology above a high minimum standard;
2. respect for the safety of patients or human volunteers who are the subjects of the research, and for their rights to information and autonomy;
3. respect for fundamental human values of a given society; and
4. scientific honesty, including full disclosure of financial conflicts of interest.

Autonomy of Subjects of Research

The underpinning Kantian principle (36) is that people should not be used as the means to someone else's ends. Medical research is, as we said, a means to better future care, but usually of people other than the research subjects. This use of one set of people for the potential benefit of another, future set of people creates ethical tension.

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Many tensions in research are the expression of conflict between competing human needs, wants, values, ambitions, and objectives, which give rise to what are termed people's *agendas* (35). The several parties to clinical trials—for example, patient, physician-investigator, sponsor—all have different agendas. If the patient's agenda is guided by his or her need to be well, the physician may share this objective through a good doctor's desire to help the patient; but both patient and physician have other agenda items. The physician-investigator's wish to help the patient is tempered by a competing desire also to be a good investigator, and the first objective of the trial is not the good of the individual patient. The tension is resolved if the patient expressly adds to his or her agenda a wish to help the physician or future patients. This, in an informed, competent, and autonomous patient, is what is meant by *consent*.

The consent of human subjects is required for whatever is done to them, in treatment and other interventions or in research. This principle, stated explicitly or implicitly in virtually all codes of ethics and documents of guidance on ethical practice since the Nuremberg trials (41), pervades medical ethics and should underpin the practice of modern medicine. It upholds autonomy, or the right to self-determination and the notion of respect for persons (36), against *paternalism,* the view that doctors know far more than patients and therefore know best, without need to consult them (5,21,27). It stands against *utilitarian* arguments, flawed but seductive, that the benefits that medical research brings to many sufficiently justify harm done to a few on the way.

Nevertheless, circumstances may erode autonomy (15,22,24), particularly that of dependent patients. Autonomy is affected, for example, by limited availability of treatment in a given society. Offers of free or improved care (25) are an *inducement* to consent ("consent or be discharged" [18]), and inducement casts doubt on how voluntary it is. That this occurs in headache trials is not in doubt; it happens because access to health care for headache disorders is limited and new treatments are haphazardly or systematically restricted. Where there is no state-supported health care for headache, the only means of obtaining treatment for some people is to enter a clinical trial. This "trade" is rarely discussed openly between investigator and patient.

Confidentiality

Support for the principle of medical confidentiality, set out in the Hippocratic Oath, is common to virtually all ethical guidance to doctors throughout history and across the civilized world (e.g., General Medical Council [19]). It is deeply rooted in pragmatism. Mutual trust and respect are essential ingredients in the doctor–patient relationship because patients who are not assured of confidentiality—and therefore fail to disclose relevant details—may not receive optimal treatment.

In research, confidentiality is commonly breached. Personal information initially collected for the purposes of clinical management is scrutinized by and shared among researchers who may have no involvement in the patient's care. This is especially true of trials monitored as part of the quality assurance of Good Clinical Practice (GCP) (see below); the recent and rather sudden expansion of pharmaceutical interest in headache has brought many such trials to parts of the world where medical confidentiality is not well protected by law. The increasing use of third-party monitors, some with lesser professional qualifications, widens the range of people having direct access to patients' medical records.

Breach of confidentiality itself requires consent. It is made acceptable by consent, but only if the scale and scope of the breach are clear to potential subjects when they consider participating in research. In particular, they "should be told of the limits to the investigator's ability to safeguard confidentiality and the possible consequences of breaches of confidentiality" (7).

Choices in Research

One of the most important current ethical concerns in headache research relates to what research is actually done. It is not obvious who makes choices, according to what agenda(s), with respect to what research is needed and what is undertaken. What the public needs (and to a lesser extent what the public wants) should be decisive. Unfortunately, except in those few countries with legally based systems of research ethics control that have strong lay representation, public opinion in these matters has no clear means for coherent expression. Least likely to be involved in choice making are people with headache.

Doctors who are aware of deficiencies in health care and interested in undertaking research to repair them are frequently unable to secure financial support for it. Government-supported research into the better management of headache has low priority. Public finance for research is available to a limited extent from charitable and patient-led organizations that have been set up with support for research into headache as one of their objectives. Although these sources of support are of significant potential benefit to headache sufferers, they are sporadic and there is no oversight to ensure justice in the sense of bringing about a distribution of fair shares to all in need (12). The pharmaceutical industry has the means to support research across most therapeutic areas but is market driven in its choices, and it is not at all evident that market forces are just. A good example is the massive pharmaceutical investment in drug development in the last 15 years, which has brought undoubted benefits to those with migraine, who are barely one fifth of all sufferers from headache.

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The majority, namely those with tension-type headache, and the most disabled, namely those with chronic daily headache, have little current expectation from research in the pharmaceutical industry.

Achieving the Right Balance in Drug Development

Ethically, the number of people exposed to an unproven drug—or to placebo—should be not excessive but sufficient to demonstrate efficacy and safety. Proof of efficacy in headache disorders requires relatively large numbers because endpoints are subjective and placebo-response rates are commonly high. Efficacy is proved only if endpoints, as well as being statistically sensitive, are clinically relevant and respect patients' values (58). Although thoughtful recommendations exist (32–34), there is no universal agreement on what are the best measures of efficacy in headache trials.

Efficacy and safety of new drugs for headache may need to be evaluated for multiple dosages in children, adults, the elderly, in specialist clinics, and in primary care. The clinical characteristics of headache (including need for and response to drug treatment) as well as the safety of treatments may differ between these groups. It is necessary to establish the minimum effective dose and, sometimes, the maximum tolerated dose. Full evaluation of headache therapy may require testing within several permutations of these circumstances. This calls on the participation of many patients, which has to be so.

Where pharmaceutical companies compete for clinical trials resources, as they recently have been doing in migraine, every trial undertaken has an opportunity cost that affects other trials that are being or might have been performed. Studies that aim solely to support marketing, if they direct resources away from trials properly investigating safety or efficacy, are unethical and in stringent national control systems are treated accordingly.

The Use of Placebo in Studies of Headache

The use of placebos in clinical trials is still debated generally (26,28,50,56). In headache, unlike some other therapeutic areas, ethical use of placebo does not depend on whether or not there are better standard treatments. The Declaration of Helsinki (67) states that "The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods." Because standard treatments do exist for both acute and prophylactic treatment of headache, this appears to rule placebo unethical (50).

But central to acceptable deliberate use of treatments less efficacious than standard treatments is autonomous patients' consent voluntarily to forego the latter. Details of those treatment options that will be foregone are part of the information that must be given to potential subjects when they consider whether or not they wish to participate. Most headaches occur transiently; where this is so, the consensual withholding of best therapy will not lead to any significant or long-term harm, especially with professional surveillance and rescue medications available (58). The International Headache Society (IHS) Ethics Subcommittee found that the use of placebo always requires justification (35), but they expressly rejected the argument, for headache trials, that "even informed patients may not be disinterested enough to decide rationally whether it is tolerable to be deprived of an accepted treatment" (50). Use of placebo is more problematic in long-term studies because consent must be continuing, not merely given at the start. Nonetheless, the issues are similar.

As for justification, placebo controls may be demanded by regulatory authorities as proof of drug efficacy, but this is not an ethical argument. On the other hand, patients may be fruitlessly exposed to risk if a trial produces equivocal results because of inappropriate experimental control. Comparison with placebo reduces the exposure to an unknown drug needed to establish its efficacy. In a particular group of patients in a trial, if a new drug and an active comparator evoke similar responses without placebo control, it is not known in that group if either has improved outcome over natural history (56) (previous evaluations of the comparator against placebo are historical). Comparison with active agents can come later if prescribers wish to know what advantage a new treatment offers over alternatives (21,28). This may help to determine what should be offered as first-line treatment but, in reality, patients can establish the advantage(s) to themselves of each by trying each one—a reasonable proposal for acute therapy. With prophylactic drugs, the situation is different in that many currently available (that might be used as comparators) are not themselves reliably superior to placebo.

The real ethical concern over use of placebo arises through the principle of truth telling and from the crucial difference between what is said to the patient and what he or she understands (58). Placebo is known to be associated with some therapeutic effect: to call it a *dummy* or *inactive substance* tells but may not impart the truth. Placebos are commonly used not only as a comparator with a trial treatment but also during run-in or wash-out periods to establish a baseline and/or identify placebo responders or noncompliers. Objections to this second use rest in part on the partial deceit needed to foil patients' presumptions as to when they might be receiving placebo (53).

Payments to Investigators

At a time of continuing high activity among pharmaceutical companies developing anti-migraine drugs coupled with a shortage of experienced clinical trials facilities, few

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trials are now carried out primarily for academic or clinical interest. Many are conducted as contract research. Investigators have little input into the protocol or prospect of authorship of publications, and perform them instead for financial compensation.

Questions must arise about research undertaken principally for payment. Paying investigators for their time spent in work under contract is not itself objectionable; the unease is about "selling" patients (58). In the United Kingdom in 1990, the Royal College of Physicians of London (52) held that "payments made on a per capita basis . . . are unethical." This was vigorously challenged by the Association of the British Pharmaceutical Industry and the guideline was soon after amended to recommend payments to practices or departments that related to workload (51). Because workload depends on numbers of patients recruited, whether this amounts to pressure to recruit, and perhaps recruit inappropriately, is not certain. But the presumption does tend to arise.

The response in some countries is a national system of rigorous oversight by research ethics committees. This requires a sound legal structure. In Denmark, for example, where such a system is in place, the Research Councils demand that payments are collected into a publicly controlled local fund (13).

Qualifications of Investigators in Clinical Research

GCP (see below) and, sometimes, legal statutes (19,63) require sponsors to ensure that appropriate skills and experience are possessed by investigators contracted to conduct their clinical trials. In many countries, no similar control is imposed upon academic research, although every investigator, whether involved in trials or other forms of clinical research, should meet the approval of a research ethics committee.

What are "appropriate skills and experience"? In all cases, investigators should be well qualified in the medical condition to be studied (6,62,67,68). Patients expect and are entitled to be appropriately managed, and this is at the heart of the professional duty of care. Whether investigators are qualified as researchers is a separate question.

During recent years, the ethical and scientific qualifications needed for research in developing countries, and in clinical genetics, and for refereeing and editing, have been the focus of reviews and new codes (38,40,47–49,61,65). These are not enough. The IHS Ethics Subcommittee considered it unethical for investigators, unless appropriately supervised, to undertake clinical research without reasonable competence in the condition being studied and, in the case of sponsored clinical trials of drugs, in GCP (35). Equally, it is unethical for sponsors to put clinical research into the hands of investigators who do not have reasonable research competence (35,63). The problem is that physicians are not, by virtue of their medical training, necessarily competent in research. Furthermore, it must be judged case by case what exactly are reasonable methodologic skills and qualifications for investigators, although it is unclear how these are acquired. Pharmaceutical companies, who commonly leave the selection of investigators to contract research organizations, appear to be influenced in their choice less by evidence of any particular competence than by expectations of enrolling sufficient numbers of subjects (6).

Headache is managed far more in primary care than by specialists; research, especially trials, should be conducted in both settings, subject to the provisos regarding competence. An investigator who is not primarily responsible for a patient-subject's clinical management has a professional duty to keep adequately informed those who are, both about the research itself and about any impact it may have on the subject's health or health care.

Quality of Headache Research and GCP Guidelines

Poor-quality clinical research is unethical because it puts patients at risk and consumes resources, with opportunity cost, without possibility of benefit to anyone (35). Data from such studies may be worthless or, worse, misleading. Clinical research undertaken to support drug registration, particularly clinical trials, is subject to well-developed codes of external quality assurance, usually referred to as GCP (29). Clinicians involved in drug development research have a professional duty (often reinforced in contract with the sponsor company) to be familiar with GCP and comply fully with its principles and practice.

GCP has been seminal in the ethical conduct of drug trials not so much because of the standards it promotes but because it introduces audit and quality assurance. It has done much to prevent or uncover fraud (46,64). Nevertheless, it has little effect in promoting good scientific (as opposed to administrative) method, and it does not stand in the way of studies with a poor rationale. The codified approach of GCP alters investigators' intellectual involvement (58). "Cook-book" clinical trials stifle intelligent thought and, conducted to protocols written no longer by investigators but by sponsor companies, deprive the former of any claim to the property in a trial (see below).

In many countries, no comparable formal codes of practice protect the quality of nonsponsored or academic clinical research, which then rests only on a combination of academic competence, diligence, and integrity. It is not evident that this is sufficient (1): studies of general and specialist medical journals have shown that researchers commonly use wrong techniques, or the right techniques wrongly, misinterpret their results or report them selectively, and draw unjustified conclusions. The IHS

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Clinical Trials Subcommittee identified the poor quality of many published trials in headache as a reason for the formulation of guidelines (32). One cause has been identified: ". . . much poor research arises because researchers feel compelled for career reasons to carry out research that they are ill-equipped to perform, and nobody stops them" (1). This remains often true even though some jurisdictions, in the Nordic countries, for example, have taken an effective stand against it.

Rights of Ownership of Data and Restrictions on Information Flow

It is commonplace that sponsored drug trial and some other research protocols provide that all data produced by the research are the property of the sponsor. Ethically, the issues arise not over ownership as such but over control (23). In multicenter studies, individual investigators without access to the whole of the data cannot judge whether they have been analyzed appropriately. Furthermore, whoever has control of data can publish them in a particular way or place, or not at all (37,39,42–44).

Whether or not these are problems in reality, there are legitimate concerns that they may be (4,16). With the expansion of interest in headache, large numbers of sponsored multicenter studies continue to be carried out, with the emphasis often on rapid completion. Investigators then move on to new studies unmindful of those completed, not all of which are ever published. Wheatley (66) placed responsibility for ensuring proper data handling and analysis on investigators, who should agree with sponsors about data management and analysis policies of multicenter trials in the protocol, which is part of the contract between them and the sponsors. The IHS Ethics Subcommittee agreed (35), and also wondered if a headache trial registry could help to answer the problem of nondissemination (17,54,55). The headache subgroup within the Cochrane Collaboration (60) is one beneficial response, and some countries have found solutions at a national level (44).

ISSUES IN HEADACHE DIAGNOSIS AND MANAGEMENT

Diagnostic methods in the management of headache patients must be based on scientific evidence of safety and accuracy, but seen in the light of costs. The marketing of diagnostic equipment before reliable evidence of these qualities has been collected is unethical. So is the use of "diagnostic" procedures that are a sham, unnecessary, or covertly experimental. Lumbar punctures have not infrequently featured in headache research under this guise; so, more recently, have various forms of imaging. Sometimes the costs of these are passed on to patients.

Because the diagnosis of most headache disorders, certainly the common ones, is based on history and examination rather than on diagnostic tests, the clinical skills these require cannot be circumvented. The IHS classification of headache in its first and second editions (30,31) has clarified the diagnostic criteria for many headache types, but these are a tool for the educated; the underlying problem leading to misdiagnosis is lack of education. In the field of headache, ignorance is widespread: in the general population as to nature, cause, treatment and prognosis; among governments and captains of industry (who pay the cost of headache) as to prevalence, consequent disability, and the economic burden; and among doctors at all levels (who receive little training in this field) as to mechanisms, diagnosis, and management. It is an unfortunate truth that whereas headache is very common both in primary care and in neurologic clinics, interest in it is not. Whatever may be patients' "rights" to timely and correct diagnosis as a prelude to timely and correct treatment (68), the reality is often a shortfall (2,59).

Therapeutic methods applied to headache patients must likewise be based on reliable evidence of effect, evaluated relative to side effects and cost. Marketing of new treatments without such evidence is unethical, whereas the use in management of many standard treatments is based on so-called clinical experience rather than on more formally adduced evidence. This has to be acceptable: the alternative would be "a state of paralysis until some piece of research is done" (14).[a]

Headache Awareness and Impact of Public Opinion

Competition for limited resources in most countries means that patients with some illnesses are less likely to receive treatment than those with others. Distributive justice calls for fair shares to all who need them, but the public perception of headache is unsophisticated, regarding it as not a disease at all or as benign and therefore deserving low (or no) priority for allocation of healthcare resources.

Such views are not justifiable in the light of the high cost of headache in lost work days and productivity (57), which, even leaving aside the humanitarian argument put up by the scale of suffering and disability (59), pleads forcefully for a larger slice of the healthcare cake than it currently receives in most if not all countries (2). Some people may receive no treatment for headache, resorting instead to self-treatment that is inappropriate or using

[a] Descartes, quoted here, saw the opportunity of acting "would not infrequently pass away before we could free ourselves of doubt." "That in order to seek truth, it is necessary to doubt . . . That we ought also to consider as false all that is doubtful . . . That we ought not meanwhile to make use of doubt in the context of life" (14).

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untested alternative methods. They are endangered by misleading advertising of proprietary treatments for headache (18), or may be induced to enter clinical trials or other research that they would not otherwise have done (see above). Of course, restricting treatment for headache frees resources for treatment of other conditions (opportunity gain), but there is a question of balance. At present this does not appear to be right.

The Need to Understand Cost Utility

Premium pricing of a new treatment may mean that many people have little real opportunity to benefit from it. (One ethical issue, beyond the scope of this chapter, is whether research to develop such treatments should be conducted in populations where this is so [38].) But important relationships between cost and effect in medical management not only occur at the level of individual patients but also raise serious issues of distributional ethics. In countries with reimbursable healthcare costs, whatever is expended on diagnostic or treatment methods that are ineffective is wasted and not available for others (opportunity cost).

Equally, it is self-evident that the appearance in the market of new, highly effective but very expensive treatments cause serious perturbations in healthcare budgets if the target population is large, as with headache. There is predictability about this. Failure to assess cost implications of this sort during a drug development program—through formal cost-utility evaluation—denies prescribers an ethical basis for rationing the treatment if simple economics dictate that it cannot be prescribed to everyone who might benefit.

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