Editorial

Psychotherapy and Psychosomatics

Psychother Psychosom 2008;77:198–200
DOI: 10.1159/000126070

Published online: April 16, 2008

Irrational Healers?

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The paper by Nierenberg et al. [1] in this issue of the journal is richly allusive. It points to the fact that some data on the effects or side effects of drugs live in a way that other data do not and outlines some mechanisms as to why this should be the case. It is important that clinicians understand the dynamics that impinge on their judgment as it is almost certainly the case that pharmaceutical companies engineer clinical perceptions based on side effect profiles. The basic company position is that clinicians have no thoughts in their minds other than those put there by us or our competitors, and in order to plant a message or dislodge those of competitors companies employ all of the heuristics outlined by Nierenberg et al., and brought out beautifully in the example they cite from the war between Pfizer and Lilly over ziprasidone and olanzapine.

The latest company technique predicated on these dynamics involves 'rating scale mongering'. Thus Pfizer at the 2007 American Psychiatric Association meeting supported a symposium 'From Clinical Skills to Clinical Scales: Practical Tools in the Management of Patients with Schizophrenia'. The practical tools were rating scales whose use would draw attention to aspects of the physical health of patients where ziprasidone could be portrayed as being superior to some other antipsychotics. The calculation appeared to be that persuading clinicians to be 'scientific' by using these rating scales would lead to sales of ziprasidone.

But there must be some further rules shaping the dynamics of prescribing than these heuristics, or alternately some of those listed must be capable of more than 1 application. Consider the dynamics of prescribing within the pediatric mental health field. Over the course of 25 years, the prescribing of stimulants to children has grown exponentially – primarily in North America. In this case, clinicians readily juggle incompatible profiles – on the one hand amphetamines and cocaine are labeled threats to civilization, while identical compounds are then given to the most vulnerable brains when other options in many cases may be just as good.

In the past 10 years D.H. has had consultancies with, been a principal investigator or clinical trialist for, been a chairman or speaker at international symposia for or been in receipt of support to attend meetings from Astra-Zeneca, Boots/Knoll Pharmaceuticals, Eli Lilly, Janssen-Cilag, Lorex-Synthelabo, Lundbeck, Organon, Pharmacia & Upjohn, Pierre-Fabre, Pfizer, Rhone-Poulenc Rorer, Roche, Sanofi, SmithKline Beecham and Solvay. In the past 2 years, he has had lecture fees and support to attend meetings from Astra-Zeneca and Lundbeck.
In the past 10 years D.H. has been an expert witness for the plaintiff in 15 legal actions involving SSRIs and has been consulted on a number of attempted suicide, suicide and suicide-homicide cases following antidepressant medication, in most of which he has offered the view that the treatment was not involved. He has been an expert witness for the NHS in a series of therapy-related cases and in 2 patent cases.

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Or consider the burgeoning prescription of antipsychotics to infants on the basis that they have a bipolar disorder. For fifty years, the antipsychotics were viewed as too dangerous to use outside secondary care and were largely restricted to those with chronic psychotic disorders where the trade-off between hazards and benefits justified treatment. Yet now a new generation of possibly even more problematic antipsychotics is being given to preschoolers, in North America, on the basis that they might have a disorder that most of the rest of the world does not believe happens in children [2].

Such willing prescription of toxic compounds for nonexistent disorders to the most vulnerable must stem from a dynamic other than the individual clinician's assessment of what the clinical trial evidence (there is no independent evidence in this domain) or their own clinical experience shows as regards hazards and benefits. In fact clinicians administering these drugs must not be registering the resulting tardive dyskinesia, marked weight gain and profound demotivation.

Trumping the evidence of a clinician's eyes is perhaps easier than we like to think. Thus the combined data from all randomized placebo-controlled trials of antidepressants, drawing on approximately 100,000 subjects, recently published by the FDA, show 5 out of 10 subjects respond to active treatment and 4 out of 10 respond to placebo [3]. Clinicians regularly take such data to indicate that these drugs work, when the data suggest that 80% of those apparently responding to an antidepressant would have responded to placebo, and only 1 in 10 people have a specific response to active treatment.

Far from following the evidence and prescribing antidepressants as a second line of treatment, after a period of judicious waiting combined with sensible advice about diet and lifestyle and basic problem solving on work-related or interpersonal issues, clinicians commonly prescribe 'at the drop of a hat'. Rather than telling someone who responds that they would most likely have done so even if a drug had not been prescribed, clinicians attribute the responses to treatment. While occasional patients may smile, knowing they have never had the treatment, the many who are misled will as a consequence be at risk of the hazards of treatment without a benefit against which these may be offset.

These antidepressant figures map precisely onto the outcomes of a Kahnemann and Tversky experiment on representativeness bias, in which experimental subjects given descriptions of a shy, retiring and bookish personality were asked to judge whether the person was a nurse or a librarian. It seems that more confident with stereotypes than with a rational analysis of the probabilities of a situation, we plump for the librarian label, even when provided with the information that the personality profile was selected from a group of 10 profiles, 8 of which were nurses and 2 librarians [4].

It may be that the availability of representative examples like penicillin bias clinicians toward believing drugs 'work', even though in the case of the antipsychotics and antidepressants there are more dead bodies in the active treatment arms of trials than in the placebo arms, which is quite different to what would be expected for penicillin.

The bias to treatment efficacy may be reinforced by recency effects stemming from hearing 'experts' claim just such evidence points to treatment efficacy, and the availability of authoritative publications making such claims in high impact factor journals. In 2004, when concerns about the efficacy and safety of prescribing antidepressants to minors surfaced, en passant a comprehensive divide was revealed between the claims made in publications, namely that the drugs were safe and effective, and what the raw data actually did show when they became available [5].

Although clinicians today travel under the banner of evidence-based medicine, if by this is meant that therapy is driven by a rational analysis of probabilities, in the absence of data it is impossible to make such an analysis. While the rhetoric is that of evidence-based medicine, clinical practice in fact conforms to a new form of eminence-based medicine. The pediatric antidepressant literature provides a good example of this new mode of practice.

The factors that give rise to a divide of the sort that has been demonstrated for the pediatric antidepressant literature must be assumed to apply to all other areas of therapeutics also. These include ghostwritten articles that appear with the best-known names in a field on their authorship line in journals with the highest impact factors in the field.

Another factor is company recruitment of distinguished figures to lecture to audiences of thousands on the efficacy and safety of drugs often for unlicensed indications. There is a striking contrast between these trade fair presentations and the academic symposia for an unbranded drug like lithium, which, through the 1960s to 1990s, even when organized by lithium's proponents, typically centered on information about the hazards of treatment and how to minimize these through monitoring. The marketing plans for the coverage of treatment hazards at meetings today in contrast at best include an

oblique detailing of the hazards that can be portrayed as occurring more commonly with a competing product and can be avoided by prescribing 'our' product. These symposia are about as likely to provide information about the common hazards of a drug class as dissenting voices are to be heard at a political rally.

While all we actually have is the appearances of scientific evidence but not the actual data from studies, prescribers do not have the means to overcome stereotypes and practice medicine based on a rational analysis of probabilities. They may claim to be following the evidence, but de facto clinicians are primarily influenced by the eminence of the authorities they listen to or journals they read and the knowledge that many of their peers will be influenced in the same way – to the point where it would seem such influence trumps the evidence of their own eyes.

Quite aside from the selective publication of trials and suppression of information, the basic interpretation of what trials show has been subverted. Randomized placebo-controlled trials originated as efforts to debunk therapeutic claims, but the force field in which medicine is now practiced has transformed them into technologies that mandate action. As a result the evidence originally designed to stop misguided therapeutic bandwagons has become the fuel for the bandwagon. Where the placebo arms of antidepressant, antipsychotic or mood stabilizer trials suggest we should not be using the drugs as readily as we do, the trials of these products, embodied in guidelines, have instead become a means to enforce treatment [6].

While the data argue against a widespread use of these drugs on the basis that they 'work' but mandate further research to identify those likely to respond specifically to treatment, for whom treatment benefits may justify risking the hazards, no research is ever done to pinpoint those likely to show a specific response to treatment. This is almost certainly because such research would concede that a much greater number are unlikely to be helped by treatment.

There is a real crisis in psychiatry at present. As Fava [7] has argued, in part this stems from the lack of independent studies. Allied to this is a lack of independent access to what data there are and an unsophisticated interpretation of the data that are available, based on conceptual models that seem increasingly inadequate. As a result clinical practice is straying ever further from the wisdom enunciated by Philippe Pinel [8] over 200 years ago: 'It is an art of no little importance to administer medicines properly, but it is an art of much greater and more difficult acquisition to know when to suspend or altogether to omit them'. If he stuck to this message, it is doubtful whether Pinel would be on the speaker's bureau for many of today's pharmaceutical companies.

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