In April 2003 [1], the UK Committee on the Safety of Medicines set up an expert working group to consider the safety of selective serotonin reuptake inhibitors (SSRIs) and in December 2003 declared that the expert group ‘... has now studied all available evidence and found that the risks of treating depressive illness in under 18s with certain SSRIs outweigh the benefits of treatment’ (Department of Health 2003). Also quoted was the chair of the UK’s Medicines and Healthcare Regulatory Agency (MHRA), who said that ‘The majority of SSRIs ... – the most commonly prescribed type of anti-depressants – are not suitable to be used by under 18s’. The regulatory language of the MHRA advice was intended as a ‘strong signal’, while falling short of an outright ban; however it has been treated as an effective ban by many practitioners and trusts around the country, and widely interpreted as such in the media. Related action by the US Food and Drugs Administration (FDA) based on the same evidence took a less assertive line, issuing ‘supplementary warnings’ only. These announcements have initiated a period of heated, often partisan debate and media attention, intensified by strongly held positions in relation to drug companies, and some confusion in clinicians about their right course of action. The MHRA has published abstracts of the evidence base on which their decision was based and the FDA has minutned further documentation of ongoing review work [2]. Further academic reviews of published and unpublished studies [3,4] have put intensive focus on the evidence base, raising key issues about the internal and external validity of the trials undertaken, the nature of data from unpublished trials and the reporting of adverse events.

At the time of writing (April 2004), the issues are far from settled, although the more work that is undertaken, the more questionable seems the evidence base on which inferences about safety and effectiveness of SSRIs in young people have been made. Whatever the final outcome, the future has raised welcome and long overdue questions about the conduct of drug trials and the evidence base for child and adolescent psychiatry psychopharmacology as a whole. Highlighting and addressing these issues could be a real value to future practice in the field.

The medicine of childhood (including child psychiatry and paediatrics) has long suffered an anomalous position in relation to prescribing. The general absence of licensing for most medications in under 18s has led child and adolescent specialists to extrapolate from adult data in treating their patients. In child psychiatry there has been characteristically a period of 3 or 4 years while medications introduced into adult practice trickle down into child and adolescent practice – often in an idiosyncratic and patchy fashion and dependent on local and national peer consensus. Given the considerable increase in general Child and Adolescent Mental Health Services (CAMHS) prescribing over the last decade and an increasingly litigious environment, it is not surprising that this working arrangement (unsatisfactory as it always was) has come under scrutiny.

The fundamental problem is the lack of good quality and purposefully designed psychopharmacological research in childhood and adolescence. Detailed evidence to the FDA specialist advisory committee [5] confirms that the FDA actually issued invitations to drug companies to undertake the studies in childhood and adolescence, which form the basis of the current debate, as a condition of conferring continuing licensing exclusivity with this age group. This may have been their motivation, but major questions have since been raised about the internal and external validity of the resulting studies. Regarding adverse effects, it was only when patient level rather than summary data from these trials were disclosed that the FDA was alerted to increased levels of ‘suicidality’ reported by patients during the trials. This had not been apparent in the summary data because the studies had classified the phenomena as ‘emotional lability’, a term which did not signal increased risk [5]. Quite apart from this apparent
reporting bias, recent reviews have highlighted the poor quality of the basic research design that elicited these unwanted effects in the first place [2]. Because of these flaws, Laughren [5] points out that it might equally be possible to make a reciprocal error of overestimating the signal of risk from these data. No completed suicide has been reported in studies on a total of 1717 patients [6]; the actual symptoms described cover a broad range of more or less specific phenomena from agitation, arousal, depressive thinking, thoughts of self-harm, to active suicidal ideation and self-harming behaviour. These are important symptoms and include an ‘activation syndrome’ with SSRIs, which has been a common observation in the clinical literature for many years. But it is still an open question as to whether all these symptoms necessarily signal increased ‘suicidality’. The FDA [2] has commissioned an extensive reevaluation of the data in relation to adverse effects, to see to what extent the phenomena initially reported as emotional lability need reclassifying, whilst acknowledging that the original data has been a common observation in the clinical literature for many years. But it is still an open question as to whether all these symptoms necessarily signal increased ‘suicidality’. The FDA [2] has commissioned an extensive reevaluation of the data in relation to adverse effects, to see to what extent the phenomena initially reported as emotional lability need reclassifying, whilst acknowledging that the original data are often so poor that even this exercise is likely to be inconclusive, a conclusion also reached by Whittington et al. [4].

However, it was not just the presence of apparent adverse effects that led to the MHRA guidance, but the presence of these in the context of a relative absence of evidence of effectiveness for all the drugs in the SSRI class bar fluoxetine. Both published and unpublished studies have been subject to searching reviews in this regard. One review [3] is highly sceptical of the internal validity and presents evidence to suggest that the authors (whom they note were funded by pharmaceutical companies) exaggerated the positive effects in the studies by selective quoting of the data, post hoc revision of primary outcomes and failure to report serious adverse effects. Some of these serious criticisms are justified by detailed reexamination of primary data, but in this partisan area one has to note that the senior authors themselves declare conflicts of interest as members of an international organization ‘aiming to reduce harm from misleading drug promotion’. A helpful metaanalysis [4] compared data from published and unpublished studies and showed evidence of publication bias in favour of positive results: data indicating effectiveness of a number of SSRIs in the published studies disappeared when unpublished data were added. The authors concluded that the evidence base is not methodologically sufficient to make conclusions regarding adverse reactions and suicidality, but that in the absence of evidence for efficacy the precautionary principle should discourage their use.

While this evidence compromising claims of effectiveness seems compelling, Whittington et al. do not address remaining concerns about the possible lack of external validity in these studies. The sampling frame was poorly characterized and may have excluded many children and adolescents who would have been prescribed these drugs in the UK (e.g. those with more complex problems). Data were gathered over a huge developmental age range (5–18 years) with no purposive stratification in relation to age or severity, both likely predictors of outcome. The upper age criteria were based on administrative factors in contracting rather than testing any biologically plausible hypothesis about age-related responses. Only five studies in childhood across the whole of the SSRI group meet the methodological inclusion criteria for Whittington et al.’s review. Given the modest effect sizes in adult SSRI studies, Laughren [5] argues that there would be a 70% probability of such a small number of studies showing negative results even if SSRIs in childhood actually had the same effectiveness as in adulthood.

Against such an uncertain evidence base, the use of the precautionary principle, while perhaps reasonable for interim action pending further data, may provide a poor basis for definitive judgement, and can throw up paradoxical and unintended consequences [7]. Without properly designed studies, we run the risk of throwing the baby out with the bathwater, of overlooking clinical situations and patient subgroups in which some of these medications may well be valuable (as much clinical experience would suggest) and depriving clinicians of treatments for some of their most ill patients. While the clinical decision-making regarding these drugs in CAMHS previously relied on extrapolation from multiple adult studies, this new recommendation is made on the basis of a small number of methodologically unsatisfactory studies in the under 18s.

**What are the lessons we can learn from this?**

The first lesson is the pressing need for properly designed and powered pragmatic studies of medications in children and adolescents, which could test the concerns raised by the MHRA and FDA data. Any such studies would need to be purposively designed around age and severity stratification (clinical experience would suggest that it is likely that over 15s with severe disorders would be more likely to benefit from antidepressants), and include sophisticated measurement techniques that would allow contextualization of the unwanted effects and other mental state phenomena reported. Such trials would arguably best involve independent academic institutions rather than being conducted solely by the pharmaceutical industry. Unfortunately, there is little tradition of the independent funding of such studies in the UK, which surely is no longer a viable position to be in.
It would be very unfortunate if the debate around this issue polarized and resulted in pharmaceutical companies withdrawing from this area of activity. A variety of medications are increasingly used in this age group, mostly off label. Surely we need a partnership approach which encourages responsible pharmacological research in children and adolescents. We should no longer have to rely on dubious extrapolations from adult practice, but generate our own research base. Not to do so risks depriving children of the potential benefits of scientific medicine. We may be able to look to new European legislation requiring drug companies to undertake this kind of research.

Given the concern about non-reporting of negative results in these studies (a concern of course which is not confined to drug trials alone), there would be an argument for allocation of central funds to conduct replications of drug company trials. Furthermore, trial methodology should include phase II dosage-finding as well as primary studies. None was undertaken in the trials reviewed by the MHRA.

Also highlighted is the anomaly whereby research undertaken by drug companies can be withheld from public view on the basis of commercial confidentiality. Potentially this means that both serious adverse effects and potential benefits of drugs are not disclosed to the wider community and that bodies such as the National Institute of Clinical Excellence, who are attempting to evaluate the evidence base, are working on partial or corrupted information [4]. There can surely be no ethical justification for this. Suggested solutions have included the mandatory registration of all trials undertaken or a condition made of ethical approval that the results should enter the public scientific domain. The scientific community is moving towards greater systemization of trial methodologies and the inclusion of registration for drug company trials could allow methodology and results to be open to public view.

There is a complex issue of evaluating what is significant harm. In effectiveness trials we are now used to thinking in terms of ‘numbers needed to treat’ or clinically relevant effect sizes rather than simple measurement of change as the most relevant endpoint analysis. Perhaps similar steps need considering in relation to the assessment of risk, with some metric for what constitutes ‘clinically significant harm’. Otherwise, an increasingly litigious culture may make us set the threshold criteria for risk in a rather different way to those for effectiveness [7]. In the SSRI case, what exactly constitutes the risk is open to debate – to what extent are the phenomena intrinsic to the disorder, a manifestation of increased arousal as a well recognized unwanted effect of the drugs, or true suicidality? It would equally be quite wrong, however, to minimize the concerning findings in these studies. I suggest the correct response is for more carefully designed and fit for purpose studies to be carried out in the target clinical populations to give practitioners a good evidence base for their practice. It is time for a step change in the way we go about funding this central area of our work and for child and adolescent psychiatry to cease to be a poor relation in terms of psychopharmacology treatment trials.

References


