Editors' view

Monitoring for harms of therapy

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The word monitor comes from the supine form, *monitum*, of the Latin verb *monere*, which has several meanings – to remind, bring to the notice of, suggest a course of action to, advise, serve as a warning to, presage. *Monere* was the causative form of the verb *meminisse*, to remember, which itself came from the putative Indo-European root *MEN*, to have one's mind aroused, with all that that implies, both religious and secular.

Mnemosyne, the Greek goddess of memory and mother of the Muses, reminds us of mnemonic and amnesia. *Minerva*, the Roman goddess of wisdom, brings to mind *mens*, the Latin mind, which gives us mental, sentimental, dementia, and *memento mori*. The Norse god *Odin* had a raven on each shoulder, one called *Hugin*, mind, the other *Munin*, memory.

A mantra was a Sanskrit instrument of the mind, a prayer or counsel; a mandarin was a counsellor to the Chinese Emperor; a maenad was an orgiastic worshipper; a mantis appears to be praying. The many words that end in – mancy are not unconnected, for they are methods whereby one can learn something by divination (Greek *manteia*).

Another Greek word, *menthenein*, to learn, gives us mathematics and various learned words – polymath, philomath, opsimath (a late learner), chrestomathy (an educative selection of literary extracts) – and the learning problem of *acatamathesia*.

And for want of a better theory, *MEN* may have given us the word man, the only creature that knows his own mind, or thinks he does.

Monitoring for harms of therapy

The purposes of monitoring are to maximize benefit and to minimize harm. We know little enough about how to monitor the beneficial effects of drug therapy and other

interventions – what the best measures are, how often to measure them, how to interpret the answers, and what to do when they change [1]. In this issue of the *Journal* Coleman *et al.* highlight issues related to monitoring for adverse effects of drugs [2]. They remind us that many Summaries of Product Characteristics provide instructions for monitoring that are incomplete or impractical; that information on harms from clinical trials is relatively sparse and may not be relevant to clinical practice. They discuss the potential application of control theory and computerized decision making systems. And they review the factors that influence the opportunities for monitoring for harms.

Monitoring based on classification

Different types of harm require different monitoring approaches. For example, one's monitoring strategy when giving intravenous adrenaline will be different from one's strategy during long-term therapy with amiodarone. Some lessons about this can be learned from considering how to classify adverse drug reactions, as demonstrated by the system known as DoTS, which is based on dose relation, time course, and individual susceptibility [3].

Dose relation

Toxic effects of drugs occur at supratherapeutic doses. Consider digoxin. Its adverse effects are mostly toxic ones; monitoring the plasma digoxin concentration can help to avoid them [4]. But monitoring techniques sometimes come in packages. One also needs to remember that certain factors, both kinetic (e.g. renal insufficiency) and dynamic (e.g. potassium depletion), can increase the concentration of digoxin at the site of action or shift the dose-response (i.e. concentration-effect) curve to the

left, increasing the risk of harm; monitoring those factors should be useful.

Collateral adverse effects occur at doses within the therapeutic range, implying that plasma concentration measurement will not be of use. In some cases they can be avoided by using relatively low doses; this is the underlying principle that mandates the lower doses of oestrogens currently used in oral contraceptives than were first used. However, monitoring of collateral effects generally needs to be directed at the harm itself (e.g. clozapine-induced neutropenia) or some biomarker of it (e.g. serum TSH in patients taking amiodarone).

Hypersusceptibility effects occur at subtherapeutic doses. It is therefore not possible to monitor for such effects other than by watching for the effects themselves and withdrawing the drug when they occur. However, spotting susceptibility factors (e.g. a history of penicillin allergy) could be classed as a monitoring technique.

Time course

The time course of an adverse effect can be a pointer to a monitoring strategy. For example, harms that occur only after the first dose of a drug (e.g. first-dose hypotension with ACE inhibitors) need not be sought subsequently (although ACE inhibitors can of course also cause hypotension during long-term therapy). On the other hand, delayed reactions (e.g. tardive dyskinesia with antipsychotic drugs) require monitoring during long-term therapy, and there is no value in monitoring early in treatment or during short courses. Clozapine-induced neutropenia affords a good example of the insight that can come from this approach. This is an adverse effect of intermediate time course – it occurs during a window of time after initial administration, in this case the first 24 weeks. During that time monitoring of the white blood cell count should be intensive (usually once a week), but thereafter vigilance can be relaxed, because almost all of those who are destined to suffer the adverse effect will have done so by then and the unaffected survivors will be at reduced risk.

Susceptibility

Some individuals are more susceptible to adverse effects than others, either generally or at particular times. We do not yet know what the overall contribution of genetic tests to the prevention of harms (as opposed to monitoring) will be, although it has so far been disappointing. For example, despite the fact that the association between thiopurine methyltransferase activity and the risk of adverse effects from mercaptopurine was described several years ago [5], methods for measuring the enzyme are not standardized [6] and optimal treatment is often not achieved [7]. On the other hand, acquired suscepti-

bility factors, such as renal impairment, can be easily monitored and can help predict which individuals are at greatest risk of adverse effects or become so during long-term therapy. This could, for example, dictate that serum concentrations of lithium should be measured, not at regular intervals, but when the patient becomes susceptible to its adverse effects, for example during a viral illness or a bout of diarrhoea [8]; however, it is still routine practice to measure the serum lithium concentration at defined intervals, and the relative benefits of the two approaches have not been compared.

Conclusion

The archaic word *mathesis*, mental discipline, has the same origin as the other thinking words with which I began. Alexander Pope used it in *The Dunciad* (1742):

Mad Mathesis alone was unconfin'd,
Too mad for mere material chains to bind.
Now to pure Space lifts her extatic stare,
Now running round the Circle, finds it square.

Of course, squaring the circle is impossible, because π is a transcendental number, as Ferdinand Lindemann proved in 1882. But there is no reason why we should not transcend the problems of monitoring for the harms of therapies by teasing out their causes and developing methods of detecting them or providing forewarning. Thinking about their classification and using the techniques outlined by Coleman *et al.* [2] should help.

References

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