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Highlights of this issue

By Derek K. Tracy

Behavioural and psychological symptoms of dementia

The behavioural and psychological symptoms of dementia (BPSD) impact almost all with this condition – and their loved ones – at enormous personal and healthcare cost. However variance in their longitudinal course, including individual symptom incidence and persistence, has not been well charted. van der Linde *et al* (pp. 366–377) systemically reviewed the topic, and found considerable heterogeneity, but nevertheless clinically relevant differences, across the assayed literature: both apathy and hyperactivity had a high incidence and persistence, depression and anxiety symptoms showed moderate incidence and low/moderate persistence, while psychotic symptoms had a low incidence and moderate persistence. When unresponsive to non-pharmacological interventions, such difficulties are often treated with antipsychotics, although there is justifiable concern about their potential for causing cerebrovascular adverse events. Quetiapine carries the lowest such risk, although its effectiveness data are less impressive in this population; risperidone has a European licence, but only for short-term (up to 6 weeks) use and where there are risks of harm to self or others. Rob Howard's team (pp. 378–384) assessed for clinically delineating risk factors. Comorbid depression and delusions were associated with a reduced risk of cerebrovascular adverse events (the former also carrying a reduced mortality risk), and treatment with anti-inflammatories with increased mortality. The findings suggest that delusions may represent a particularly attractive risk–benefit therapeutic target; the medication's short-term licence also fits with van der Linde *et al*'s data that they have a lower tendency to persist.

Drug harms and unexpected benefits

Prescribing patterns may vary considerably but clozapine remains our go-to medication for treatment-refractory psychosis, though curiously there has been a lack of meta-analysis of its effectiveness in this particular population. Siskind *et al* (pp. 385–392) rectify this with the first such comparison of both first- and second-generation medications. Across 21 papers covering 25 comparator compounds, clozapine was superior to all other drugs at treating positive symptoms in refractory illness in both the short and longer term; benefits in managing total and negative symptoms were only seen in the short term. High baseline psychotic scores were associated with better outcomes. Clozapine's superiority is softened by the fact that in this cohort the number needed to treat is 9, and the authors advise that if no clear benefit is seen by 6 months, then it should be replaced by a drug with a lower side-effect profile. A cautionary note is rung by Robin Murray and colleagues (pp. 361–365), who challenge our common practice of keeping individuals on antipsychotics in the longer term. This is generally what guidelines recommend, but we are also faced with established data on longer-term drug harms as well as concern about potential loss of effectiveness through supersensitivity of dopamine D_2 receptors. They argue that up to two-fifths of those whose symptoms remit after a first episode should be able to achieve good longer-term outcomes with no, or very low-dose, antipsychotic use, and that we should regularly consider the benefit–risk ratio for individual patients and aim to slowly reduce medication doses to the lowest level that prevents distressing symptoms.

Lithium inhibits the intracellular enzyme glycogen synthase kinase-3 (GSK-3), one of the postulated ways through which it affects positive therapeutic change in bipolar affective disorder. However, GSK-3 dysfunction is also linked to the pathogenesis of some cancer types, so might lithium have an unexpected additional clinical function? Huang *et al* (pp. 393–399) retrospectively evaluated a Taiwanese National Health Insurance research database, comparing the risk of cancer development in those on lithium with those on anticonvulsant medications. Fitting with the cellular data on GSK-3, patients with bipolar affective disorder treated with lithium showed a significantly lower risk of developing cancer, and the benefits were dose-related.

Antidepressants: numbers and placebo

Traversing well beyond psychiatry's borders, there has been widespread concern about the prescribing of antidepressants. Kaleidoscope (pp. 444–445) looks at the problem of those inappropriately receiving them, the growing placebo effect in research trials, but also the staggering challenges of untreated depression – US data showing that only a quarter who need it receive any treatment. Perhaps the apposite issue is the appropriateness, rather than the number, of prescriptions. Do prescribing figures actually align with public perceptions? McCrea *et al* (pp. 421–426) explored selective serotonin reuptake inhibitor prescribing in the UK over the past 20 years or so. In the six years between 1995 and 2001, such prescriptions approximately doubled. However, countering the public narrative on the topic, thereafter the rate remained stable until the study end-point of 2012. Another supposed tenet of this class of drug has been that response is related to illness severity, although some meta-analyses have suggested that the issue is of a waning placebo effect in more serious episodes rather than the medications being more effective *per se*. Rabinowitz *et al* (pp. 427–428) re-evaluate this with trial- and patient-level data from 34 randomised placebo controlled trials. Trial-level data supported previous findings, but the patient-level data ran contrary to this, showing that initial depression severity had no significant effect on drug *v.* placebo difference.

All of which feels like a perfect point to segue to Joanna Moncrieff's very stimulating selection of ten books (pp. 437–439) that have influenced her thinking.