

Kaleidoscope

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The majority of people treated with antidepressants receive them in primary care, but there are limited data on medication maintenance or discontinuation in this setting. Nevertheless, much of the public discourse centres on primary care practices, with debate on ‘over-medicalisation of sadness in life’ and concern about the doubling of the prevalence of antidepressant prescriptions over the past couple of decades (in truth, much of the latter is due to longer treatment regimens, better aligning to national guidelines). Lewis et al¹ undertook a pragmatic double-blinded randomised controlled trial across 150 UK general practices, recruiting 478 participants (the mean age was 54 years and three-quarters were women). All had a history of at least two depressive episodes and had taken antidepressants for at least 2 years but now felt well enough to consider stopping them. Only those on therapeutic doses of citalopram, sertraline, fluoxetine or mirtazapine were included, owing to the frequency of prescription of these antidepressants in primary care and their more limited discontinuation symptoms, to help mask blinding. Participants were either continued on treatment or put on a tapered discontinuation programme over several months via a pill placebo. Adherence to this across the following year was 70% and 52% in the respective groups. By the 52-week primary cut-off point, 39% of the maintenance group had relapsed, compared with 56% of the discontinuation cohort. By the end of the study, almost two-fifths of those in the discontinuation arm had been recommenced on medication. These data remind us that, unfortunately, relapse is common in depression whatever one does; clearly, they also show that many people can discontinue medication safely, but remaining on treatment enhances outcomes. The findings thus do not definitively guide the patient or clinician in ‘what to do’, but they help inform such discussions with best evidence on relative risks. It is particularly helpful to have such research in primary care, where the majority of such conversations will occur, and with non-specialised patient cohorts more reflective of ‘real world’ practice.

A major concern about antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), is that they increase suicidal behaviour; what are the latest findings on this? Lagerberg et al² pulled data from a Swedish health register for over half a million individuals aged 6–59 who had an initial SSRI prescription issued between 2006 and 2013. A clever aspect was a within-individual design, comparing suicide attempts a year before and a year after medication commencement in the same person to account for the confounder of ‘selection into treatment’ (namely, those chosen for study inclusion are in parallel at greater risk of the adverse outcome of self-harm). The highest risk of suicidal behaviour, when compared with a 30 day period a year earlier, was in the month before starting an antidepressant. This risk reduced in the month following instigation and continued to fall over time as the medication was continued. This was seen across all age groups – including the young – and also after stratifying for a history of past suicide attempts. How can one square this with existing findings of greater risk associated with commencement of SSRI treatment, especially in adolescents? The authors argue that such work was typically undertaken in randomised controlled trials with short duration of follow-up and specific patient criteria – excluding those with past suicide attempts or comorbid substance use – reducing their generalisability to real-world settings. In particular, given how relatively ‘rare’

suicidal acts are compared with depression, many trials are fundamentally underpowered to provide good data on this topic. Clearly, one needs caution and careful monitoring when initiating any medication, particularly when working with individuals who are vulnerable and at risk. The trial also found that although SSRIs reduced the risk, at the 1 year follow-up, they had not brought it back down to baseline levels seen a year before treatment. Further, it was not designed to determine causality, and it remains possible that SSRIs might precipitate suicidality in some individuals. However, these latest data, from a very large, well-powered data-set, move the needle away from antidepressants increasing suicide risk and very much towards their being preventative.

Insulin therapy was a notorious intervention in psychiatry’s past, so we were intrigued by a paper linking insulin resistance to predicting the occurrence of major depressive disorders (MDD).

Writing in the *American Journal of Psychiatry*, Watson et al³ note that insulin resistance has previously been linked to depression, but the authors take this further by exploring whether surrogate markers of this – specifically, a high triglyceride–HDL (high-density lipoprotein) ratio, ‘prediabetes’ (measured through fasting plasma glucose) and central obesity – are associated with the subsequent development of MDD. Over 600 individuals without any prior history of depressive or anxiety disorder were enrolled and followed up for 9 years. The presence of any of the three markers at the outset was associated with greater rates of subsequently developing MDD, as was the development of prediabetes in the first 2 years. To quantify this, just a moderate increase – defined as a one-unit alteration in the triglyceride–HDL ratio – equated to an almost 90% increase in the rate of developing depression in the subsequent 9 years. It is an obvious question to ask how these conditions are linked, and indeed there is bidirectionality, with depression being a risk factor for type 2 diabetes. One can anticipate that for some there might be potential common psychosocial factors around lifestyle, and socioeconomic and educational disadvantage. Animal models also show putative shared pathogenesis, with insulin resistance dysregulating glucocorticoids in the hypothalamic–pituitary axis, promoting neuroinflammation and dysregulating mitochondrial function. Pro-inflammatory cytokines in turn can reduce serotonin levels, neurogenesis and synaptic plasticity. The challenge is whether clinicians might be able to pragmatically utilise these links, perhaps as part of primary care screening and risk assessment, as a further incentive to try to keep such factors in check through lifestyle interventions. The authors note that in rodents, treatment of insulin resistance has been shown to reverse depressive symptoms; however, we don’t foresee an imminent return to insulin therapy in humans just yet.

To enhance vaccination uptake, nudging (as opposed to overt legislation or didactic teaching) has emerged as a subtle way of changing behaviour by positive reinforcement, attributed to behavioural economics and popularised by Thaler and Sunstein’s 2008 book.⁴ However, its *prima facie* appeal – especially relevant to the psychosocial sciences – is not without criticism, not least because experimental support for some of its key wins (notably, around public health interventions for better nutrition) have been shown to be fraudulent (<https://statmodeling.stat.columbia.edu/2021/02/07/nudgelords/>). One of the most pressing public health problems is vaccine hesitancy. Dai et al⁵ examine a randomised controlled nudge experiment using text messaging to improve uptake of Covid-19 vaccines. Using a Californian health database of 154 253 people eligible for Covid-19 vaccination, those who were routinely contacted by UCLA Health were then randomised to groups that received one, two or no reminder text messages. Furthermore, 93 354 patients were randomised to a control (hold-out) arm (18 749), a basic text reminder (18 629), an ‘ownership’ text reminder

(18 592), a basic text reminder with a video (18 757) or an ‘ownership’ message with a video (18 627). The ‘ownership’ message was designed to convey a sense of personalisation and ownership of the vaccine process (i.e. emphasising that the vaccine had just become available for that individual and encouraging them to ‘claim’ the dose). The video condition included a reminder text with a link to a 2 min vaccine information video (the hypothesis being that more information about the vaccine might help increase uptake). Further, to reduce inconvenience associated with obtaining the vaccine, all types of message included a direct link to a scheduling website (so that the reminder could be almost instantaneously actioned on the part of the vaccine candidate). The primary outcome was whether participants scheduled the first of their vaccine doses at UCLA Health within 6 days of the text messages. Within 6 days of the text message reminders, around 7.2% of the control hold-out group had made an appointment for the vaccine dose. Adding an information video to either of the text messages (basic versus ‘ownership’) made no statistical difference to uptake, and in the basic message groups 12.78% and 12.37% (with and without a video) of participants booked an appointment. By contrast, the ‘ownership’ message groups had 14.2% and 14.11% uptake (with and without a video), which was statistically significantly different from that in the basic message groups, suggesting that the tone of the message (a ‘nudge’ strategy) provided an approximately 2% increase in uptake. This differential pattern of results was also found in those who booked appointments within 4 weeks of the first text message. From the original pool recruited, 67 092 people who had not responded to the first text were sent a second reminder. Averaged over all four message types (with/without video, basic versus ownership), this intervention resulted in an increased likelihood of booking a first vaccine dose in 6 days from the text message by 1.65 percentage points relative to the control arm. To paraphrase Lieutenant Frank Drebin, change hurts ... Oh, sure maybe not as much as jumping on a bike with the seat missing, but it hurts. Nevertheless, in their conclusion, Dai et al extrapolate their findings to the US population, estimating that the ownership-themed intervention could induce a further 1.42–1.74 million extra people to obtain a vaccine dose within a month of receiving the reminder.

Finally, Martin Luther King Jr taught us that ‘Riot is the language of the unheard’. When large groups of people come together in destructive protest, the discourse from politicians and the media usually centres on the idea of a few bad apples and the senseless, often counterproductive, losses sustained by communities. This certainly serves to move the focus from the message of the rioters and dampen the legitimacy of those calls for change, but is it accurate? Within social science, the leading explanation for riotous behaviour is relative deprivation. Unlike economic and other forms of absolute hardship, relative deprivation is a subjective feeling that occurs when people believe they deserve more than they have, often as they see others around them with more. The resulting resentment is thought to increase the likelihood of engaging in collective destruction, though clear support for this direct link has been lacking as most insight has been gained from correlational population data. Motivated by the 2011 London riots, Dezechache and

colleagues⁶ used an agent-based simulation game called ‘Parklife’ to investigate factors involved in rioting. The goal of the game was to build the best park by adding valuable additions such as trees and benches through collective work. Participants were seated within the same room while accessing the game through individual devices, and could watch the progress of their team and the opposition on a large shared screen. Tapping on an individual device was added to the taps of their randomly selected team members and manifested in the team progress, which was displayed on the large screen. In the ‘equal game’, four taps were required to build each new park item – or to destroy an item within the other team’s park. So each individual could choose to pro-socially work toward building their park, work to sabotage the other park (which takes constructive taps away from their team) or not tap at all. Within the ‘unequal game’, for one team it would take eight taps to build something for their park, but the cost to destroy an item of the other team’s remained the same. Within these unequal games, more acts of collective aggression occurred and were associated with feelings of frustration at the unfair treatment of their group. Of course, these destructive acts harmed team progress so were not rational *per se* but an expression of inequity. Random assignment ensured that no individual level variable could be blamed, while computational modelling showed frustration to be a key explanatory variable in this sabotaging behaviour, which rose in concert with group identification. Interestingly, the vandalising behaviour of individuals emerged within the group context, in that destruction only occurred when other team members were involved in building park items, a naturally formed labour distribution: it is unclear whether individuals understood their parts in collective action. Regardless, this experimental approach again lays to rest the idea that rioting can be laid at the feet of violent individuals and instead comes about via relative deprivation and social identification. As we sit within the shadow of the Pandora Papers, in a world with shockingly unequal wealth distribution, we must acknowledge the societal impacts and psychological burden that real and perceived inequity causes.

References

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