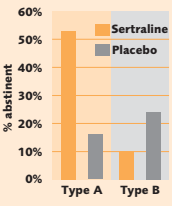
6.4 Alcohol dependence typology may help decide which drugs to prescribe

Findings Two US studies found that drugs with an opposing impact on the brain help different types of alcoholics curb their drinking, raising the prospect that a simple classification can be used to match patients to the drug elements of their treatments.

Serotonin transfers messages within neural networks implicated in mood, impulse control, depression and in the pleasurable effects of alcohol. The SSRI (selective serotonin reuptake inhibitor) antidepressant sertraline increases serotonin activity, while the anti-sickness medicine ondansetron partially blocks it. Each study randomly allocated treatment-seeking alcoholics to counselling plus one of these drugs or a placebo and attempted to identify alcoholics for whom serotonin dysfunction was most likely to be a factor in their alcoholism, and correcting it a factor in their recovery.

In study ❶ placebo or 200mg daily of sertraline were prescribed for 14 weeks to 100 alcoholics who had not drunk for at least three days. Patients were divided into type A (not severely dependent, late onset alcoholism, relatively free of psychological problems) or type B (severely dependent, early onset, depression and other forms of psychopathology). Unexpectedly, patients thought to have normal serotonergic function (type A) benefited from sertraline. The effects were statistically significant and clear cut. On the drug they typically drank on virtually 0% of days and 53% were completely abstinent during the trial, compared to over a fifth of days and 16% on placebo. In contrast, type B clients (thought to have serotonin dysfunction) tended to do *worse* on sertraline.



In study ❷, for 11 weeks 271 patients received different doses of ondansetron or continued on placebo. Alcoholism onset before age 26 was thought to be related to serotonergic dysfunction. As expected, only these patients benefited from ondansetron, maximally at a dose equivalent to about 0.64mg daily. At this dose, compared to placebo there were significant reductions in the amount drunk overall and per drinking day and more patients maintained abstinence, regardless of whether they had stopped drinking first. Impacts were only moderate, perhaps partly because during the lead-in patients had already nearly halved their alcohol consumption. In contrast, late onset alcoholics tended to do *worse* on ondansetron than on placebo.

In context Together the studies suggest that by augmenting serotonin levels, SSRIs reduce drinking in late onset/type A alcoholics, while serotonin blockers such as ondansetron do so in early onset/type B alcoholics, and that reversing the pairing worsens outcomes compared to placebo. We could have greater confidence in this neat pattern if the studies had used the same classification system. It remains an open question whether findings in study ❷ would have remained broadly the same if it had used the typology in study ❶. We know that the reverse was not the case.

Unless depression is clinically severe, the impact of antidepressants has generally been found to be small compared to other aspects of the treatment package and the patient's desire to tackle their drinking. However, earlier studies might have failed to find effects because all the patients were lumped together in the analysis. As opposed to amount and frequency of drinking, no study has demonstrated that any serotonergic medication significantly reduces the risk of relapse to alcohol dependence. By design, just over half the patients in study ❶ had a history of diagnosed major depression. If they were the ones who benefited from sertraline, rather than the findings being new and surprising, the study is an extension of earlier work showing the value of antidepressants in clinically depressed alcoholics.

LINKS Nuggets 5.2 5.1

Study ❷ is only the second trial of ondansetron for alcoholism. Both left a question mark the drug's impact on very heavy drinkers. The study's main significance is the finding of beneficial effects in patients (early onset) presumed to be extremely difficult to treat. This presumption does not square with rapid and large cuts in alcohol consumption even before medication had started, and with high treatment compliance. Exclusion criteria could have meant that the study failed to net the most difficult-to-treat patients.

Both studies were rigorously designed. However, treatment was conducted in clinical research centres and patients received structured, high quality counselling and therapy which probably helped raise compliance to relatively high levels. Outside this context many more patients may simply have failed to take the pills.

In line with the featured studies, previous studies have reported numerous side-effects from SSRIs; though not medically serious, these may be distressing and affect quality of life. Ondansetron causes minimal adverse side-effects.

Practice implications In the absence of clinical depression, SSRI treatment is not helpful for the higher risk/severity alcoholics characterised as type B. For this type of patient, at the right dose ondansetron can augment the impact of psychosocial therapy. It remains unclear whether simply under-26 age of onset of alcoholism or a typology based on severity of drinking and psychological problems is the best way to identify such patients. For lower risk/severity alcoholics, the SSRI sertraline may augment the effect of high quality psychosocial treatment.

Given the incidence of side effects from SSRIs and the patchiness of the data, there seems no case for widespread deployment in alcoholism treatment, and ondansetron has been studied in too limited a range of patients and in too few studies. Evidence for other relapse prevention agents such as naltrexone and acamprosate is far stronger. However, further exploration of both types of drug is warranted in certain patients. Clinicians trying these relatively unproven strategies should carefully monitor the reactions of their patients and provide high quality therapy to help maintain compliance and as a treatment in its own right.

Featured studies ❶ Pettinati H.M., *et al*. "Sertraline treatment for alcohol dependence: interactive effects of medication and alcoholic subtype." *Alcoholism: Clinical and Experimental Research*: 2000, 24(7), p 1041–1049 ❷ Johnson B.A., *et al*. "Ondansetron for reduction of drinking among biologically predisposed alcoholic patients. A randomized controlled trial." *Journal of the American Medical Association*: 2000, 284(8), p. 963–971. Copies: for both apply Alcohol Concern.

Contacts ❶ Helen Pettinati, Addiction Treatment Research Center, University of Pennsylvania School of Medicine, 3900 Chestnut Street, Philadelphia, PA 19104-6178, e-mail pettinati@research.trc.upenn.edu ❷ Bankole A. Johnson, University of Texas Health Science Center, 7703 Floyd Curl Drive, Mail Stop 7792, San Antonio, TX 78229-3900, USA, e-mail bjohnson@uthscsa.edu.

Thanks to Dr Bankole Johnson for his assistance.