	Citalopram (mg/day)	Escitalopram (mg/day)	Fluvoxamine (mg/day)	Paroxetine (mg/day)	Sertraline (mg/day)	Duloxetine (mg/day)	Venlafaxine (mg/day)
Step 1	20·0	10·00	50·0	20·0	50·00	60·0	75·0
Step 2	10·0	5·00	30·0	10·0	25·00	30·0	37·5
Step 3	6·0	3·00	20·0	7·0	15·00	15·0	20·0
Step 4	4·0	2·00	15·0	5·0	10·00	10·0	12·0
Step 5	3·0	1·50	10·0	3·0	7·50	6·0	7·0
Step 6	2·0	1·00	5·0	2·0	5·00	4·0	5·0
Step 7	1·0	0·50	2·5	1·0	2·50	2·0	3·0
Step 8	0·5	0·25	0·0	0·5	1·25	1·0	2·0
Step 9	0·0	0·00	..	0·0	0·00	0·0	1·0
Step 10	..	..	..	..	..	..	0·0

Hyperbolic reductions are calculated based on a desired 10% reduction in serotonin transporter occupancy per step, following the Michaelis–Menten equation: Dose = (Occupancy / B_{max}) × (ED_{50}/ (1-Occupancy / B_{max}), where B_{max} is the maximal occupancy possible, ED_{50} is the dose with 50% occupancy, and both are determined per drug on the basis of PET data (appendix pp 14). Depending on occurrence and tolerability of antidepressant withdrawal symptoms, which might still be occurring when following these steps, the interval between steps (or dosages) can be adjusted via shared decision making by the patient and physician. This Taskforce does not consider prolonged use of any dosage of these discontinuation steps without further attempts of discontinuation as being rational pharmacotherapy. SNRI=serotonin–norepinephrine reuptake inhibitor.

***Table*: Steps in dosing to discontinue SSRIs and SNRIs in case of one or more risk factors for acute withdrawal syndrome**

might either be bearable or, if not, would prompt a return to the dosage of a step earlier when no antidepressant withdrawal symptoms were noticed, followed by a slower discontinuation. This policy resembles the nomogram provided by Horowitz and Taylor,[1] which is clinically very helpful.

Because of paucity of evidence to exactly guide clinical recommendations, we strongly advocate shared decision making and careful, repeated evaluation of the hyperbolic dosing steps. Advocating shared decision making could have been more explicit in the manuscript.

In 2018, Bockting and colleagues[4] showed that the combination of preventive cognitive therapy (PCT) and maintenance antidepressants was superior (in terms of relapse prevention) to antidepressant maintenance therapy or PCT with discontinuation of antidepressants. In the same study, relapse rates were similar between antidepressant maintenance therapy and PCT with discontinuation of antidepressants. In a meta-analysis of four studies, Kuyken and colleagues[5] showed that mindfulness-based cognitive therapy was superior to maintenance antidepressants. These publications emphasise the need for careful evaluation of the risk of recurrence or relapse before antidepressants are discontinued, and for initiating preventive psychotherapy to reduce risk of recurrence.

For more on the **OPERA project** please see https://opera-project.nl

We agree with Horowitz and Taylor[1] that empirical evidence regarding the discontinuation of antidepressants is urgently needed. Research should address: (1) the prevalence of antidepressant withdrawal symptoms in clinical populations discontinuing antidepressants, (2) systematic identification of risk factors for antidepressant withdrawal symptoms and their relevance being determined in prospective studies, and (3) the relative advantages of different dose-reduction regimens (eg, comparing mini-tapering and micro-tapering, and different timings of dose steps). In the ongoing OPERA project, the first two of these issues will be addressed, for the third, large collaborative randomised trials still need to be initiated.

We declare no competing interests.

Henricus G Ruhe, Annemieke Horikx, Mariëlle J P van Avendonk, Bart F Groeneweg, Hèlen Woutersen-Koch, on behalf of the Discontinuation of Antidepressants Taskforce
h.g.ruhe@gmail.com

Department of Psychiatry, Radboud University Medical Center, Nijmegen, Netherlands (HGR); Donders Institute for Brain, Cognition and Behavior, Radboud University, Nijmegen, Netherlands (HGR); Dutch Association for Psychiatry, Utrecht, Netherlands (HGR); Royal Dutch Pharmacists Association, The Hague, Netherlands (AH); Dutch College of General Practitioners, Utrecht, Netherlands (MJPvA); MIND Landelijk Platform Psychische Gezondheid, Amersfoort, Netherlands (BFG); and Dutch College of General Practitioners, Utrecht, Netherlands (HW-K)

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Authors' reply

We thank Sudhakar Selvaraj and colleagues[1] for their interest in our work. They offer several critiques of the relevance of PET occupancy data to withdrawal effects. However, we think their claim that changes in plasma levels of drug would not be associated with withdrawal symptoms has little evidential support. The more abrupt reduction in plasma levels of antidepressants with shorter half-lives is understood to cause their more severe and quick-onset withdrawal symptoms.[2] Selvaraj and colleagues state that a study by Michelson and colleagues[3] shows no correlation between change in blood concentration and withdrawal symptoms for any individual SSRI; however, they also found "percentage reduction in plasma concentrations across drug groups was statistically significantly correlated with new adverse events."[3] This suggests that the study was underpowered to find an effect for individual agents—an

effect which became clear when the three SSRIs were grouped together.[3] Additionally, reduced brain receptor exposure to antidepressants is likely to be the key factor in withdrawal symptoms, and plasma concentration might not accurately reflect brain exposure because of a number of individual pharmacokinetic effects, another limitation to this analysis.[3]

Selvaraj and colleagues claim that a hyperbolic relationship between antidepressant dose and serotonin transporter occupancy, obtained by PET, would not hold with long-term treatment. We concur that neuroadaptation to long-term use of antidepressants is likely[2] (which, in turn, is the probable basis of withdrawal symptoms). However, the law of mass action would not be suspended by such a change; it would simply entail a right-shifting of the dose-response curve, while maintaining its overall hyperbolic shape. The law of mass action is a foundational pharmacological principle describing a steep increase in effect at small doses of drug, flattening out as receptors become increasingly saturated. Log transformation of the x-axis in older textbooks, yielding linear-appearing graphs for intermediate doses, can obscure this fact.

Selvaraj and colleagues question the analogy to benzodiazepine tapering: but as the law of mass action applies across species, drug classes and receptor targets, we hold that the principle of tapering according to the biologically meaningful unit of receptor activity, as for benzodiazepines, makes more sense than tapering linearly according to dose.

We agree that such a paucity of research into withdrawal symptoms is regrettable, so that potentially non-representative samples are the best data available on severity of the symptoms. Nonetheless, uncertainty over the exact incidence of withdrawal effects is perhaps exaggerated: the meta-analysis cited found an incidence of 44%,[1] compared with 56% in a previous analysis.[2]

We welcome Henricus Ruhe and colleagues'[4] thoughts on our paper, and concur with many of their conclusions—rate of tapering should be jointly decided with patients, some patients might tolerate intervals shorter than one month (which might be determined empirically) and preventative psychotherapy should certainly have a role in the process.

Golo Kronenberg and colleagues[5] suggest that so-called nocebo effects might have a role in antidepressant withdrawal. Although this notion cannot be discounted, the presence of withdrawal effects in double-blind trials, as well as the presence of quite particular symptoms such as electric shocks suggest the contribution might be small.

Minimisation of the scale and severity of withdrawal alongside somewhat vague prescriptions for tapering[1] is not a rational way forward. Instead, further study of the incidence, nature, timing, and severity of withdrawal symptoms and testing of plausible tapering regimens, and ways to individualise them, is required. If regulators do not require manufacturers to do such studies for licenced products, the government and independent researchers will have to step in. Energetic leadership in this area will assure patients that their concerns are being heard and addressed; an approach that will help to maintain, or regain, trust.

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*Mark Abie Horowitz, David Taylor
mark_horo@hotmail.com

Prince of Wales Hospital, Sydney, NSW 2031, Australia (MAH); and Institute of Pharmaceutical Science, King's College London, London, UK (DT)

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Smoking cessation in people with serious mental illness

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In *The Lancet Psychiatry*, Simon Gilbody and colleagues[1] report the effect of an intervention that aimed to increase tobacco abstinence in people with serious mental illness. The intervention was designed to improve the utilisation of available smoking-cessation services of the UK National Health Service by smokers with schizophrenia and bipolar disorder who were interested in cutting down or quitting smoking. It consisted primarily of home visits by mental health nurses who delivered a modified, manualised smoking-cessation intervention. Communication with primary care providers regarding attempts to quit and abstain was facilitated, but prescription of pharmacotherapeutic cessation aids was left to the discretion of the primary-care physician.

Uptake of nicotine replacement therapy was common, although it is not clear what proportion of participants used single or dual nicotine replacement therapy, what the duration of use was, or to what degree use was expressly encouraged by those delivering the intervention. Varenicline use was rare (3% of patients, with varenicline-use data unknown in 40%) and the prevalence of abstinence was low.

Gilbody and colleagues[1] make an important contribution, showing high uptake of an intervention tailored to be acceptable to those with serious mental illness. However, the established very low proportion (4%) of smokers with schizophrenia with behavioural treatment alone who quit,[2] and the remarkable benefit of