

**Table. Association of Self-medication Drinking With Persistence and Recurrence of Alcohol Dependence at Follow-up by 12-Month Alcohol Dependence Status at Baseline Among Participants With History of Lifetime Alcohol Dependence at Baseline**

|                                        | OR (95% CI)                                                                                  |                                                                                  |                                                                                     |
|----------------------------------------|----------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
|                                        | Persistence of Alcohol Dependence <sup>a</sup><br>(Lifetime or 12-mo Dependence at Baseline) | Persistence of Alcohol Dependence<br>(Lifetime and 12-mo Dependence at Baseline) | Recurrence of Alcohol Dependence<br>(Lifetime Without 12-mo Dependence at Baseline) |
| Unadjusted <sup>b</sup>                | 5.39 (3.98-7.28) <sup>c</sup>                                                                | 2.73 (1.78-4.17) <sup>c</sup>                                                    | 3.92 (2.31-6.64) <sup>c</sup>                                                       |
| Propensity score adjusted <sup>b</sup> | 3.45 (2.35-5.08) <sup>c</sup>                                                                | 2.05 (1.18-3.57) <sup>d</sup>                                                    | 2.61(1.43-4.74) <sup>e</sup>                                                        |

Abbreviation: OR, odds ratio.

<sup>a</sup> This definition of persistent dependence was used in the original article.<sup>1</sup>

<sup>b</sup> Unadjusted analyses were based on 1547 participants and propensity score-adjusted analyses were limited to 1485 of these participants whose propensity scores fell within the common support range.

<sup>c</sup>  $P < .001$ .

<sup>d</sup>  $P < .05$ .

<sup>e</sup>  $P < .01$ .

for these analyses included the 1547 drinkers with lifetime alcohol dependence who reported mood symptoms at baseline, provided information regarding using alcohol to self-medicate their symptoms, and were reinterviewed at follow-up. All analyses took into account NESARC survey weights and other design elements. Analyses were further adjusted by propensity scores using inverse probability of treatment weighting, as described in our article. We conducted stratified analyses in which we assessed the association of self-medication with alcohol dependence at follow-up separately among those who did and did not meet the 12-month (current) alcohol dependence criteria at baseline. Of the 1547 individuals with lifetime alcohol dependence, 573 (36.1%) met the criteria for current alcohol dependence at baseline, and 974 (63.9%) did not meet the criteria for current dependence. Self-medication drinking was associated with alcohol dependence at follow-up among both individuals who did as well as those who did not meet the criteria for current dependence at baseline (adjusted odds ratio = 2.05; 95% CI, 1.18-3.57;  $P = .01$  and adjusted odds ratio = 2.61; 95% CI, 1.43-4.74;  $P = .002$ , respectively) (Table).

We also tested the interaction of current alcohol dependence at baseline with self-medication drinking in a model predicting alcohol dependence at follow-up. A significant interaction term between self-medication and current alcohol dependence at baseline would suggest differences in the relationship of self-medication with alcohol dependence at follow-up according to whether individuals met criteria for current alcohol dependence at baseline. The interaction term for current alcohol dependence at baseline with self-medication did not meet criteria for statistical significance ( $F_{1,61} = 1.16$ ;  $P = .29$ ).

In summary, these additional analyses conducted in response to Boschloo and colleagues' suggestion indicate that drinking to self-medicate mood symptoms was associated with both the persistence of alcohol dependence among those with current alcohol dependence at baseline and with the recurrence of dependence among individuals who had met the criteria in the more remote past but who were in remission at the time of the baseline interview. Possible explanations for differences in findings from the article by Boschloo and colleagues<sup>2</sup> include the methods used as well as the sample assessed (self-medication among

drinkers with mood symptoms vs mood and anxiety symptoms as predictors).

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### Early Medication Discontinuation on Long-term Recovery Outcome in First-Episode Psychosis

**To the Editor** We read with interest the recently published study by Wunderink et al<sup>1</sup> in this journal. It confirms previous evidence that drug-naïve patients may respond to doses of antipsychotic medication at the lower end of the recommended range<sup>2</sup> and goes further suggesting that patients in the dose reduction/discontinuation (DR) group have better long-term functional outcomes. Nevertheless, there are several methodological issues regarding that study as highlighted next.

First, both groups were similar in their intervention. Data from their initial 18-month follow-up trial<sup>3</sup> show that 51 of 65 patients (78.5%) in the DR group could not discontinue drug treatment (only 14 patients [21.5%] accomplished discontinuation successfully) vs 58 of 63 (92.1%) in the maintenance treatment (MT) group. In the long term, only 8 patients in the DR group and 3 patients in the MT group sustained treatment discontinuation during follow-up. Moreover, according to Wunderink et al, MT “was carried out...with preferential prescription of low-dose second generation antipsychotic.”<sup>3</sup> Differences in doses between groups were significantly different, although with elevated standard deviation and arguable clinical significance (mean [SD], DR group, 2.2 [2.7] mg vs MT group 3.6 [4.1] mg). Second, the differences in functional outcomes could be explained by nonpharmacological factors. There is a baseline difference between groups in occupational status, which, though not statistically significant ( $P = .07$ ), implies a trend and is an important factor regarding functionality. The same applies for differences in schizophrenia diagnosis. There was no blinding of the primary outcome, which could bias the results concerning the functional assessment.<sup>4</sup> Furthermore, follow-up was naturalistic and unblinded, so there could be a difference in unmeasured psychosocial aspects, such as community care and number of visits, as Wunderink et al acknowledged. Finally, it is not clear if Wunderink et al used the second version of the Groningen Social Disabilities Schedule, cited in their first publication,<sup>3</sup> or the first version. The former (Groningen Social Disabilities Schedule II) had a questionable inter-rater reliability in international studies.<sup>5</sup> It is unclear to what extent the Groningen Social Disabilities Schedule represents an objective measure of functioning.

In summary, the lack of blinding and the baseline differences between groups, with large numerical differences in pivotal variables, might have biased the study results. The ideal design would have been a randomized clinical trial with fixed-dose antipsychotic therapy using an objective measure of functioning as the primary end point. A misinterpretation of the study results might end up with patients with first-episode psychosis (and perhaps patients with multiple episodes as well) being undertreated and having a poor clinical and functional outcome.

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**To the Editor** Wunderink et al<sup>1</sup> studied the long-term effects of early dosage reduction or discontinuation (DR) of antipsychotic medication vs maintenance treatment (MT) on recovery in patients with remitted first-episode psychosis. It makes an important contribution to the literature and has intriguing clinical implications. However, we would like to clarify some issues before concluding the longitudinal benefits of DR over MT in the study.

Although the type and dose of antipsychotics used in the Wunderink et al study<sup>1</sup> were reported during the last 2 years of follow-up, information such as treatment adherence and adverse effects are lacking. Medication nonadherence is common in patients; thus, medication prescribed may not equate to medication taken, which has important implications on remission, relapse, and recovery. As demonstrated in Figure 2 in the Wunderink et al article,<sup>1</sup> the DR group had a more stable pattern of medication dose than the MT group in the last 2 years. This suggests that patients in the MT group may have a more fluctuating course of illness. However, we believe that medication information recorded during the last 2 years may not be sufficient in addressing better recovery at 7 years in the DR group. The control for these and other possible confounders, such as the availability of psychological and psychosocial support and treatments over the illness course, is essential. However, Wunderink et al only mentioned in the Discussion section that the 2 groups had no differences in any of the conceivable confounding variables.

The differences in diagnostic categories in the 2 groups may be a plausible explanation toward the significantly better recovery and functional remission in the DR group. In fact, more patients in the MT group were diagnosed with schizophrenia (51%) and fewer with delusional disorder (7.8%) than their DR counterparts (36.5% and 15.4%, respectively). Previous re-

search has suggested that delusional disorder may be a separate entity with distinct etiology and outcome, different from other psychoses and affective disorders.<sup>2,3</sup>

Additionally, there were no statistical differences between the 2 groups in terms of social functioning and subjective quality of life at 7 years. We therefore wonder if the significant differences in functional remission and recovery may be largely attributed to the inclusion of more patients who were medication free on follow-up (10 of 11 in the DR group and 3 of 6 in the MT group) instead of suggesting that the DR group had superior social functioning at 7 years. It would also be interesting to explore if quality of life is more related to symptomatic remission than functional remission or recovery.

Given that the original Wunderink et al study<sup>4</sup> had demonstrated that the DR group had 2 times the relapse risk than the MT group at 18 months, the current nonsignificant finding after 7 years (mean [SD], MT group: 1.35 [1.51] vs DR group: 1.13 [1.22]) needs further explanation. Whether DR group patients (who experienced discontinuation in the original study) were more likely to have MT in the subsequent years, especially when they may have relapsed after the original study, is unknown. The lack of medication data over the entire 7 years may have limited the ability to address this important issue.

Finally, we propose to highlight the important finding that only those who successfully discontinued medication in the original study significantly and independently predicted successful DR during the last 2 years of the 7-year follow-up. It may be too early to conclude that patients who had early medication discontinuation fared better in recovery at 7 years than those who continued medication. It demands for future studies that can address these concerns and examine if early medication discontinuation can really benefit patients with first-episode psychosis in the long run.

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**In Reply** Undurraga et al comment on 3 methodological issues they perceived in our article.<sup>1</sup> First, they state that both interventions were similar because ultimately only a small number of patients discontinued treatment and the mean doses used were arguably significantly different.

1. The aim of the study was to reduce antipsychotic dose. The ultimate form of dose reduction is discontinuation. Though maybe not impressive, it was relevant to 21.5% of patients who achieved it, against 7.9% in the control condition. Undurraga et al overlook short-term relapse rates: twice as high in the dose-reduction strategy.
2. Apart from discontinuation, patients who did not discontinue took lower doses, too. And, we believe that the difference in mean dose is clinically significant: dopamine blockade is more pronounced at 3.6-mg than 2.2-mg haloperidol equivalents. The slightly elevated standard deviation in the maintenance treatment group is logical, compared with the smaller variance of a reduced dose.
3. Operative guideline-recommended maintenance strategy implies lower-range dosing. Differences would have been more pronounced if the maintenance treatment group had received a higher dose, a strategy we fortunately abolished.

Second, Undurraga et al suggest functional outcomes could also be explained by baseline differences; they mention no blinding of the primary outcome and a subjective and unreliable outcome measure (Groningen Social Disabilities Schedule II).

1. At baseline, groups did not differ.<sup>2</sup> Undurraga et al are mistakenly referring to 2-year outcome. The trending effect of dose reduction on vocational status was already there after 2 years. The proportion of patients with schizophrenia diagnosis was not different at baseline. We diagnosed patients at baseline and did not revise diagnosis. At baseline, schizophrenia was probably underdiagnosed because duration of illness was often too short to assign a schizophrenia diagnosis.
2. We are not aware of any way to accomplish “blinding of the primary outcome.” Probably Undurraga et al mean blinding of the original treatment conditions. Raters were probably not aware of these. We acknowledged patients might have informed raters during assessment. We deem it highly unlikely that this would account for the magnitude of the effects. Differences in psychosocial aspects are also unlikely to be related to outcome, because of randomization per site. No differences appeared during the first 2 years of follow-up.
3. Interrater reliability of the Groningen Social Disabilities Schedule II was satisfactory as reported in the 2-year follow-up article.<sup>2</sup> The Groningen Social Disabilities Schedule II is to be preferred above less specified scales.<sup>3</sup> The scale is indeed subjective in the sense that level of deviation from norms and expectations of the reference group have to be scored by the (trained) interviewer. We think such an instrument is most closely related to the concept of recovery. But this might warrant a special discussion.

Finally, we strongly disagree with Undurraga et al that the ideal design would be a fixed-dose randomized clinical trial.

We used an individualized approach reducing the dose as much as feasible without recurrent symptoms; some patients discontinued, but most continued to receive a low dose. A fixed-dose approach puts the cart before the horse, returning to non-personalized treatment.

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## Diabetes Risk Potentially Underestimated in Youth and Children Receiving Antipsychotics

**To the Editor** Analyzing a Medicaid database, Bobo et al<sup>1</sup> found an alarming 3-fold increased risk of diabetes in children and youth receiving antipsychotics, compared with those receiving other psychotropic medications. Increased risk was evident within the first treatment year, increased further with cumulative dose, and remained elevated 1 year after antipsychotic discontinuation. The disturbing findings of this landmark study provide strong evidence for an increasing burden of metabolic disease risk for young people treated with antipsychotics, because the impact of early-in-life diabetes on health and life expectancy concerns all. A further sobering issue is that in this study, as in clinical practice,<sup>2</sup> patients received antipsychotics for conditions where antipsychotics are either not the sole treatment option or where efficacy is unproven.

While an absolute rate of an additional 16 new cases of type 2 diabetes per 10 000 patient years was reported, with a number needed to harm of 633,<sup>1</sup> the study may not have accurately measured diabetes risk. First, controls were receiving other psychotropic medications, some of which also increase diabetes risk. Second, diabetes ascertainment was based on antidiabetic medication use, a serious limitation. Only 1 in 16 participants had “diabetes screening procedures.” Without routine screening, only cases with symptomatic frank hyperglycemia were likely to be detected, since the renal glycosuria threshold exceeds 17 mmol/L. It is likely that many cases were not detected and noncases

were misidentified. The study’s observation that risk increased in the first year suggests antipsychotics either rapidly induce diabetes or rapidly progress undetected diabetes or prediabetes.

Nonetheless, the clinical implications of this article are, in our view, clear. Antipsychotics should be used with caution in children and youth, where indicated, and only when non-pharmacologic interventions and lower-risk nonantipsychotic options have failed. If still required, a low-risk antipsychotic should be selected. Further, routine metabolic complication monitoring is mandatory, as are lifestyle interventions to prevent diabetes.<sup>3-5</sup> Monitoring and preventive intervention should be components of the standard of care, instigated at antipsychotic initiation. Supporting the need for parity of physical health expectations for youth with severe mental illness, the Healthy Active Lives (HeAL) Declaration details principles to prevent premature cardiometabolic disease ([www.iphys.org.au/media/HeAL\\_declaration.pdf](http://www.iphys.org.au/media/HeAL_declaration.pdf)), just as the St Vincent Declaration benchmarked diabetes care 2 decades ago.

All clinicians should be concerned about the preventable disease burden associated with antipsychotic use. Until risk-neutral antipsychotics are developed, we urge all medical practitioners to engage in protecting the physical health of young people with mental illness.

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