EDITORIAL

# Early schizophrenia: skilful management of medication†

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†See editorials on pp. 78–79 and 85–87, this issue.

**SUMMARY**

It is premature to dismiss the usefulness of long-term treatment of schizophrenia with antipsychotics. Skilful management of medication is paramount with these patients.

**DECLARATION OF INTEREST**

J.C. has advised and lectured at meetings sponsored by the manufacturers of several antipsychotics.

The enthusiastic embrace by Moncrieff (2015, this issue) of Wunderink *et al*'s 7-year follow-up of a 2-year randomised controlled trial (RCT) of treatment for first-episode psychosis (Wunderink 2013) is understandable. But any eagerness to dismiss the usefulness of long-term treatment with antipsychotics is premature. The results are counter-intuitive and seem to have puzzled the authors themselves and to invite speculative explanations.

The two pivotal trials on which current recommendations for the management of a first episode of schizophrenia-like illness are based were conducted in the 1980s in the UK, at London's Northwick Park Hospital (Crow 1986), and in the USA (Kane 1982). They show two main findings (Table 1). First, after remission of symptoms, continuation of medication for 1 year leads to a much lower rate of relapse than switching to placebo; the number needed to treat (NNT) for avoiding relapse is 2–4. This advantage was most impressive in those (consenting) patients whose adherence to medication was assured by depot treatment; in that study (Kane 1982) no patients on antipsychotic medication relapsed in 1 year. Second, about 37% of patients who switched to placebo in the UK study and 59% in the US study did not relapse within the following year; furthermore, in the UK study 30% had not relapsed within 2 years.

In retrospect, these studies had obvious limitations involving low statistical power and, in the US study, both small numbers and mixed diagnoses. Neither study could identify which patients were likely to remain well without medication after the first episode.

In those who had been ill for more than 1 year before treatment, all had relapsed within 2 years on placebo; this evidence stimulated work to reduce the duration of untreated psychosis (DUP) or untreated illness (DUI), such as the creation of early intervention teams within all community mental health services in England, under the National Service Framework (Department of Health 1999).

Beyond relapse and concerning function (educational, occupational and social achievement), the Northwick Park study concluded, perhaps prophetically: 'Although this part of the study was not controlled, the excess of achievers on placebo as compared with active medication is compatible with the possibility that the price of the reduced risk of relapse conferred by neuroleptics is a decline in achievement' (MacMillan 1986).

Hence, many guidelines recommend continuing medication for at least 1 year after remission of symptoms, and then giving the opportunity to

**TABLE 1** Placebo-controlled RCTs of continuation treatment for 1 year after remission of first-episode non-affective psychosis

| Study | Groups | *n* | Randomisation | No relapse by 1 year, % | Difference, % | NNT (95% CI) | Comments |
|---|---|---|---|---|---|---|---|
| Crow *et al*, 1986 | Antipsychotic | 54 | 1 month after discharge | 62 | 25 | 4 (3–14) | 62% on depot treatment<br>All with schizophrenia |
| | Placebo | 66 | | 37 | | | |
| Kane *et al*, 1982 | Antipsychotic | 13 | After 4 weeks of remission | 100 | 41 | 2 (2–6) | All on depot treatment |
| | Placebo | 17 | | 59 | | | |

RCT, randomised controlled trial; NNT, number needed to treat.



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**TABLE 2** 1-year placebo-controlled RCT of antipsychotic, after 1 year of stability following first-episode psychosis

| Study | Groups | *n* | Discontinued because of side-effects, *n* | No relapse by 1 year, % | Difference, % | NNT (95% CI) | Comment |
|---|---|---|---|---|---|---|---|
| Chen *et al*, 2010 | Quetiapine | 89 | 18 | 59 | 38 | 3 (2–4) | Many dropped out of quetiapine group |
| | Placebo | 89 | 8 | 21 | | | |

RCT, randomised controlled trial; NNT, number needed to treat.

gradually reduce and even discontinue medication in those remaining well. Such guided reduction requires careful medication management with skilled reviews.

## After 1 year of remission

For those who remain stable on medication for 1 year after remission of an episode of non-affective psychosis there is an RCT (Chen 2010) comparing the antipsychotic quetiapine (up to 400 mg/day) with placebo for a further year (Table 2). Patients selected represented those expected to have the best chance of successful discontinuation. There was a very low rate of avoiding relapse on placebo, only 21%. Despite the large difference in relapse rates (38%), changes in occupational status during the study did not differ statistically between the two treatment groups. The high rate of drop-out from the trial owing to side-effects with quetiapine points to the need for drugs that are better tolerated.

## Continuation *v.* guided reduction of dose after 6–12 months of remission

In their initial study, Wunderink *et al* (2007) reported an open (non-masked) RCT in which people recovering from a first episode of non-affective psychosis with 6 months of remission received further medication for 18 months in one of two ways: either continuing a fixed dose of antipsychotic ('maintenance treatment'), or guided according to symptoms in a dose reduction with the possibility of eventual discontinuation ('dose reduction/discontinuation') (Table 3). Of the 257 eligible patients, 128 (about half) improved sufficiently and agreed to be randomised. In the study group, 45 of 128 (35%) reported comorbid substance misuse.

Patients received 'frequent monitoring, low-threshold access to services and patient education about prevention of relapse and recurrent symptoms'. In the context of the dose reduction/discontinuation group this might be better called skilful management of medication.

Only 35 (54%) actually discontinued medication during dose reduction/discontinuation and 21 (33%) had to start taking it again. Thus, only 14 (roughly 22%) were off medication at the end of 2 years. Of those on maintenance treatment, 5 patients (8%) discontinued but 2 restarted.

For those receiving prescriptions (mainly risperidone or olanzapine) there was little difference in medication doses between groups at the start or end of the trial, or between the start and end, except that quetiapine doses rose from about 423 mg/day to 541 mg/day, reflecting the lower than expected potency.

The group treated with a possibility of discontinuation had more relapses than the maintenance group (difference: 22%; NNT = 5), and there were no advantages of the discontinuation strategy in terms of functional outcomes.

A similar conclusion was reached by Gaebel *et al* (2011) (Table 3). After 1 year of antipsychotic maintenance treatment, patients who were stable after a first episode were randomised openly to receive either 12 months of further maintenance treatment or stepwise drug discontinuation and targeted intermittent treatment ('stepwise discontinuation'). Twenty-five per cent of patients (15/59) would not accept the randomised

**TABLE 3** RCTs comparing maintained dose *v.* guided dose reduction after remission of first episode of non-affective psychosis

| Study | Groups | *n* | Duration | No relapse, % | Difference, % | NNT (95% CI) | Comments |
|---|---|---|---|---|---|---|---|
| Wunderink *et al*, 2007 | Dose continuation (maintenance treatment) | 63 | 18 months | 79 | 22 | 5 (3–16) | Mainly oral risperidone or olanzapine |
| | Dose reduction +/– discontinuation | 65 | | 57 | | | |
| Gaebel *et al*, 2011 | Dose continuation (maintenance treatment) | 23 | 12 months | 100 | 19 | 5 (3–45) | ICD-10 schizophrenia Stable 1 year on antipsychotic |
| | Stepwise discontinuation and intermittent treatment | 21 | | 81 | | | |

RCT, randomised controlled trial; NNT, number needed to treat.

condition, so out of 96 eligible patients only 44 were finally included in the analysis. This caused imbalance in the baseline characteristics and required a modification of the intention-to-treat principle.

Patients on maintenance treatment had to maintain the drug regimen from the end of the first year for the whole second year. In those assigned to stepwise discontinuation, the antipsychotic was completely removed in a stepwise fashion over a period of 3 months (at the most). With stepwise discontinuation, 42.9% had marked clinical deterioration compared with 0% for maintenance treatment. To manage this deterioration, patients were carefully re-assessed every 2 weeks. Nevertheless, 19% relapsed and were admitted to hospital.

Patients in the maintenance treatment group scored better at study endpoint on the Clinical Global Impression – Severity of illness (CGI-S) scale, the Positive and Negative Syndrome Scale (PANSS) positive and general scores, and social functioning. With intermittent treatment, cumulative drug dose and side-effects were lower and about 50% of patients did remain stable.

Thus, in both studies there was no apparent benefit in guided discontinuation over maintenance treatment, although some patients did remain stable on lower doses with fewer side-effects.

## Follow-up after 7 years

The results of further follow-up of Wunderink *et al*'s study participants 5 years later (Wunderink 2013) caused some surprise (McGorry 2014).

Of the original 128 patients, 103 were available for follow-up. During the intervening 5 years, there were no specified differences in the management of the two groups. Nevertheless, the mean antipsychotic dose (in haloperidol-equivalent mg) during the final 2 years of follow-up in patients originally receiving guided dose reduction/discontinuation (2.20 mg/day) remained significantly lower than the dose in those who had received maintenance treatment (3.6 mg/day). Thus, the effects of randomisation on clinical management persisted throughout the 7-year period. The authors described the dose reduction/discontinuation strategy as 'fitting in with the current concept of the clinician–patient relationship'. Twenty-two people were on no medication for the final 2 years. At the end of the study, 14/52 from the dose reduction/discontinuation group and 11/52 from the maintenance treatment group were on no antipsychotic (Table 4).

Overall, similar numbers of patients experienced a relapse in the two groups, but first relapses occurred sooner in the dose reduction/discontinuation group.

Of the original 128 people, recovery (defined as meeting the criteria for symptomatic and functional remission) was seen in 30 of the 103 available for interview, and more often (21/52 or 40.4%) in the group originally in dose reduction/discontinuation than in the group on dose continuation (maintenance treatment) (9/51 or 17.6%). The difference was in the number with functional remission; by contrast, there were no differences in symptomatology (PANSS scores).

Side-effects were not measured beyond 18 months. They had been equally low in both groups in the first 18 months, but long-term side-effects might account for the differences in functional recovery after 7 years.

## Discussion

During first episodes, doses of antipsychotics required for treatment are lower than subsequently: for example, haloperidol at 3 mg/day, risperidone at 2–3 mg/day and olanzapine at 10 mg/day (see Schooler 2005; McGorry 2011).

For long-term treatment, patients with schizophrenia can be maintained on lower doses of antipsychotic medication than those used to control the episode of acute illness. For at least some of these patients, continuous dopamine $D_2$ receptor blockade above 65% occupancy (i.e. the lower end of the established therapeutic window for acute treatment) is not always necessary for maintenance treatment (Uchida 2014). More than half of patients taking risperidone long-acting injections maintained clinical stability without

**TABLE 4** **7-year outcome, 5 years after RCT of maintenance *v.* guided reduction of dose**

| Study | Groups in initial study[a] | *n* | Recovered (at year 7), *n* (%) | Difference, % | NNT (95% CI) | Comment |
|---|---|---|---|---|---|---|
| Wunderink *et al*, 2013 | Dose continuation (maintenance treatment) | 51 | 9 (17.6%) | 22.8 | 5 (3–18) | Dose reduction/discontinuation group received lower doses in years 6–7 |
| | Dose reduction +/– discontinuation | 52 | 21 (40.4%) | | | |

RCT, randomised controlled trial; NNT, number needed to treat.
a. Wunderink *et al* (2007).



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achieving continuous dopamine $D_2$ receptor occupancy exceeding 65% (Ikai 2012). Reductions in doses of risperidone and olanzapine in stable patients with schizophrenia improved cognitive function and extrapyramidal symptoms over 28 weeks without a worsening in psychopathology (Takeuchi 2013).

Thus, it is appropriate to manage schizophrenia with carefully monitored dose reductions during follow-up, being prepared to raise the dose again should symptoms emerge. A balance needs to be found between the fortnightly detailed assessments in Gaebel *et al* (2011) using determined reductions, and the less intensive reviews required with continued dosage regimes. Probably the skilful medication management required for the guided dose reductions of Wunderink *et al* (2007, 2013) represent a more ideal approach.

For those whose illness does not remit with such treatment, clozapine should be considered, with all the additional side-effects it entails. For patients who will not agree to medication and do not warrant compulsory treatment, cognitive–behavioural therapy may alleviate some symptoms (Morrison 2014).

## Conclusions

The main finding of the Wunderink *et al* study is that after 7 years, 30 people from the original 128 with a first episode of non-affective psychosis were identified as being in recovery, with symptomatic and functional remission; of these, 25 were on no medication at that time. This group represented about half of the patients eligible for the study. The findings tell us that skilful management of medication is important in helping patients to achieve more complete remission of functional impairments after a diagnosis of schizophrenia-like illness.

It remains advisable for patients with a first episode of schizophrenia or other non-affective psychosis to continue on medication for at least 1 year after remission of the episode and/or discharge from hospital. A proportion of patients who remain well 1 year later may not require further antipsychotic medication, but there is no reliable way of identifying these, other than by a gradual discontinuation of medication. Those with a longer initial DUI or with comorbid substance misuse are less likely to remain well for long without medication. For those requiring medication to remain well, adherence is important; the medication is not effective unless it is taken, and side-effects must be recognised. The management of dosage, choice of antipsychotic and achievement of adherence require close clinician–patient relationships with skilful clinical management, as does advice to the families and carers.

In some settings, substance misuse with cannabinoids, stimulants and 'legal highs' is so common that there may be individuals with first episodes of psychosis for whom abstinence from those substances is even more important than establishing long-term antipsychotic medication. Nevertheless, mentally ill young people are so vulnerable that providing them with treatment, including antipsychotic medication, is a fundamental right.

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