

Accessed from: http://hdl.handle.net/1959.13/1042586
Varenicline plus healthy lifestyles in people with a psychotic disorder
In press, Annals of Clinical Psychiatry (accepted 27.02.2012)

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Acknowledgements:
Funding and supply of varenicline for this study was provided by Pfizer Pty Ltd as part of an
investigator-initiated study. The company had no input into design, analysis or write-up of the study
and no individual involved in the study received any financial or other incentives regarding the study.
We thank Kate Filia for assistance with follow-up assessments, Charlotte Ross-Harris for data entry,
Jill Williams for assistance with study design and Jayashri Kulkarni and Anthony de Castella for
support.
Abstract
Objective: To explore the efficacy and safety of varenicline as an adjunct to a healthy lifestyles intervention for smoking cessation amongst people with a severe mental illness

Methods: Open study using varenicline as an adjunct to a healthy lifestyles intervention in 14 smokers with a psychotic illness

Results: Overall, smoking cessation rates were 36% at 3 months and 42% at 6 months. The most commonly reported side effects were sleep disturbance and nausea. These tended to occur early in the course of treatment and patients responded to general measures of support and reassurance. Of the 14 participants, only one dropped out because of psychiatric problems; two further patients dropped out because of other side effects.

Conclusions: Varenicline appears to be an effective adjunct to a healthy lifestyle intervention for smokers with a psychotic illness. However, whilst the results of the current open study are encouraging, replication in an adequately powered randomised controlled trial is required before definitive conclusions can be drawn.
Introduction

Whilst rates of cigarette smoking among the general population have declined significantly over the past 20 years in many Western countries in association with successful public awareness campaigns and legislation, people with mental illness do not seem to have benefited from these general approaches, with very high rates of smoking expressly in those with severe mental illnesses such as schizophrenia [1,2]. This trend remains after controlling for a range of socioeconomic factors. Smoking is associated with serious morbidity, lower quality of life and earlier mortality among people with psychosis compared with the general community. Whilst some successful smoking cessation interventions have been developed for this group of individuals, there remain major gaps in terms of addressing this particular problem in people with psychotic illnesses, who are also at significant risk of other risk factors for cardiovascular disease (eg., obesity, diabetes) and who are thus particularly in need of effective smoking cessation interventions [3].

A number of investigators have evaluated various combinations of psychological and pharmacological interventions to assist quitting in smokers with psychosis. These have been usefully reviewed [4], and include individual- and group-based psychoeducation [5], nicotine replacement [6,7], bupropion [8,9] and bupropion in combination with nicotine replacement [10,11,12]. Our own work in this field sets the foundations for the current study. Thus, Baker et al [13,14] conducted a large controlled trial of a smoking cessation intervention among individuals with a psychotic disorder. In that study, 298 heavy smokers were randomly assigned to treatment as usual or to an 8 session, individually administered smoking intervention. The intervention consisted of nicotine replacement therapy (NRT) and cognitive-behaviour therapy (CBT). Compared to the control condition, a significantly higher proportion of smokers who completed all treatment sessions had stopped smoking at 12 months (point prevalence abstinence, 19% vs 7%). In a subsequent open trial, we [15,16] have produced and piloted a more comprehensive treatment program (the “Healthy Lifestyles” programme) for people with psychosis, which addresses other lifestyle factors (notably diet and exercise) as well as cigarette smoking. Treatment sessions over three months were offered to all participants following a baseline assessment, with follow-up occurring at 15 weeks. Four sites recruited 43 participants. There was a statistically significant reduction in smoking between pre and post-treatment, with 19% point prevalence abstinence at post-treatment assessment. The average number of cigarettes per day reduced from 31 per day to 17 (p<0.001). These data are encouraging, but abstinence rates of 19% still leave many individuals with schizophrenia with a problematic smoking habit, and new pharmacological interventions have the potential to enhance abstinence rates.

One such alternative agent is varenicline, which has proven efficacy in randomised controlled trials against placebo, NRT, and bupropion for smoking cessation [17-21]. Varenicline binds with the α4β2 neuronal nicotinic acetylcholine receptor, where it acts as a partial agonist. Its binding both alleviates symptoms of craving and withdrawal, and reduces the rewarding and reinforcing effects of smoking by preventing nicotine binding to α4β2 receptors. However, there have been significant concerns about potential psychiatric effects of treatment with varenicline, with depression and suicidality being the most well publicised [22]. In fact, the perceived risk of these outcomes is probably exaggerated [23], but a high degree of concern about its use in people with an established mental illness remains in the minds of clinicians and patients. Furthermore, single case reports have suggested the potential of varenicline to worsen psychotic symptoms in some individuals with schizophrenia [24] and induce mania in some individuals with bipolar disorder [25].

The study reported here was aimed at exploring the efficacy and safety of varenicline as an adjunct to a psychosocial intervention, in people with schizophrenia, schizoaffective disorder and bipolar disorder. Our hypothesis was that varenicline plus Healthy Lifestyles would be effective and well tolerated as a smoking cessation intervention among people with psychotic disorders.

Methods:

We conducted an open trial of varenicline plus our established Healthy Lifestyles intervention, among people with psychotic disorders. Patients were recruited via their case managers at the two community mental health centres associated with St Vincent’s Mental Health Service, Melbourne, Australia. Our target was 15 patients, based on pragmatics of funding and follow-up arrangements; one declined to participate after screening, leaving a total of 14.
Inclusion Criteria
(1) Aged 18 years and over; (2) diagnosis of a psychotic disorder (e.g. schizophrenia, schizoaffective disorder, bipolar disorder, based on the Mini International Neuropsychiatric Interview [26]) and on stable psychiatric medication for at least three months; (3) current heavy smoker (at least 15 cigarettes per day).

Exclusion Criteria
(1) Non-psychotic illness; (2) smoking fewer than 15 cigarettes per day; (3) non-English speakers; (4) people with organic brain diseases; (4) an unstable psychiatric (e.g., actively suicidal, as per clinical judgement) or medical condition (e.g., uncontrolled diabetes); (5) people with any specific contraindication to the use of varenicline (apart from having a mental illness).

Assessments
All assessment instruments are widely used in mental health and/or tobacco treatment research and practice. Demographic characteristics and previous treatment history were collected from participants at the initial assessment. The following instruments were administered at each weekly visit:
- **Tobacco use**: Opiate Treatment Index (OTI) [27] to estimate average daily use of tobacco; the Fagerstrom Test for Nicotine Dependence (FTND) [28]; expired carbon monoxide using a Bedfont Smokelyser; and the Minnesota Nicotine Withdrawal Scale – Revised (self and observer rating) [29].
- **Psychiatric Symptomatology**: Brief Psychiatric Rating Scale (BPRS) [30], a well-validated measure of psychotic symptoms; Beck Depression Inventory (BDI) [31], a well validated self-report measure of depressed mood, with a specific item on suicidality; the Young Mania Rating Scale (YMRS) [32], a widely used and validated assessment of manic symptomatology.
- **Side effects**: At each visit, participants were asked whether they have experienced any symptoms that they considered to be side effects of the varenicline; they also filled out our standardised side-effect check-list (available upon request from the authors).
- **Safety checks**: To ensure safety, we added to the above outcome measures specific safety monitoring. This included, at each weekly visit, the Columbia Suicide Severity Rating Scale. In addition, in between each study visit the therapist delivering the intervention (DH) made telephone contact with each participant, as a quick check of wellbeing.

Formal assessment was performed at baseline and at 3- and 6-months post-baseline. These assessments were conducted by trained research assistants who were not involved in the delivery of the smoking cessation intervention and who did not have prior knowledge of the participants. Each participant was offered $30 for the initial assessment and each post-treatment assessment occasion, as reimbursement for their time and out of pocket expenses such as travel or parking fees. All procedures were approved by the St Vincent’s Hospital (Melbourne) Human Research Ethics Committee.

The Intervention:
(a) **The non-pharmacological component**: The intervention was adapted from our established manual guided “Healthy Lifestyles” programme [15,16]. It was delivered as 6 once-weekly sessions of 1-hour duration, followed by three 1-hour booster sessions at weeks 8 and 10 and 12. Specific components of therapy include case formulation and feedback from assessment, psychoeducation, motivation enhancement, mood/craving monitoring, mindfulness training, cognitive restructuring (identifying and managing unhelpful automatic thought patterns), enhancement of non-smoking related activities, pleasant events scheduling, coping with cravings (cigarettes), problem-solving, refusal skills and relapse prevention and/or management. During each therapy session, discussion and skills practice focussed on the particular unhealthy behaviours identified as most important/problematic by the
participant. Opportunities were taken by the therapist to integrate messages/skill development about other lifestyle factors as appropriate. Self-help material was provided throughout the treatment period, according to the unhealthy lifestyle behaviour being discussed in the session. The therapist delivering the intervention (DH) was experienced in delivery of the Healthy Lifestyles intervention and received training and weekly supervision from AB.

(b) The pharmacological component: Varenicline was provided to participants at each visit. Dose titration was: 0.5mg daily for days 1-3; 1mg daily for days 4-7, and 1mg twice daily (the target dose) from days 8 to 84.

Results
Table 1 provides a synopsis of the age, gender and primary psychiatric diagnoses of the intervention group, as well as the most prominent reported side effects. The main side effects included sleep disturbance and nausea. Only one patient dropped out because of psychiatric issues: she had a severe recurrent bipolar disorder with psychosis, and experienced depressed mood, agitation and irritability along with suicidal ideation and ceased the medication after four days; her psychiatric symptoms stabilised within a week and she continued smoking around 25 cigarettes a day. Another patient, who had successfully ceased smoking, stopped his varenicline after three weeks due to constipation but recommenced it after his urge to smoke was exacerbated and he feared a return to smoking. Two further patients ceased medication because of ongoing nausea (one at three weeks, one at three months).

Table 2 shows baseline and six month outcomes. There was a significant reduction in cigarettes smoked per day, with carboxymeter-confirmed abstinence being achieved in six patients. Analysis of only those who were not abstinent at 6-months follow-up showed a significant reduction in number of cigarettes smoked per day. Of interest was that, whilst observer-rated nicotine withdrawal increased from baseline to 6-month follow-up (p< 0.05), patients themselves reported a decrease in this rating (p=0.02). There were no significant changes from baseline to follow-up on the BDI (pre: 9.2 (SD 7.0); post: 8.1 (SD 8.1)), YMRS (pre: 3.8 (SD 5.5); post 4.9 (SD 6.0)), or BPRS (pre: 35.6 (SD 5.0); post: 39.8 (SD 8.9).

Discussion
This open study showed that varenicline, in association with a comprehensive healthy lifestyles intervention, was associated with a substantial decrease in cigarette smoking amongst a heterogeneous group of patients with psychotic disorders. Abstinence was achieved in 42% of the participants at the six month time-point. Side effects were mostly non-psychiatric (sleep disturbance, nausea) and transient; only one patient (with bipolar disorder) dropped out because of a severe worsening of depression, with suicidality.

A number of published studies have specifically assessed the use of varenicline in people with a mental illness. Stapleton et al [33] conducted a pre-post comparison of patients treated with NRT before the availability of varenicline, compared with varenicline-treated patients; varenicline appeared to be effective and well tolerated. However, the Stapleton et al [33] study was not designed primarily to address the mental illness issue, and the non-pharmacological part of the intervention was not tailored to those with a mental illness. Also, only a small proportion had a mental illness of any type, and only 7 patients (0.2% of the sample) had a psychotic illness. Purvis et al [33] performed a retrospective review of 50 veterans who had received varenicline. Overall 30% quit smoking and 70% failed either because of lack of effectiveness or inability to tolerate the medication. The proportion of those with a mental illness was higher in the failure group (57%) vs. the success group (27%) (p<0.001). Four patients discontinued because of mood and behavioural problems: all had an established mental illness. McClure et al [34] analysed smoking outcomes and side effects associated with varenicline in attendees at a smoking cessation clinic. Participants with a probable history of major depression were more likely than
those without such a history to report tension/agitation, irritability/anger, confusion or depression at 21 days (p<0.05) and depression and anxiety at 3 months (p<0.01); however, smoking cessation rates did not differ between the groups. Smith et al [35], in a study of varenicline in 14 patients with schizophrenia and schizoaffective disorder, reported no significant exacerbations in psychopathology ratings; side effects included nausea, dry mouth, sleepiness and shaking but only two patients discontinued treatment and nine of the remaining 12 reduced the number of cigarettes smoked, although only one was abstinent at the end of the trial. Finally, Weiner et al [36] performed a double-blind placebo controlled trial of varenicline in 9 patients with schizophrenia or schizoaffective disorder and again found no worsening of psychotic symptoms but constipation, nausea and insomnia were reported side effects; varenicline was associated with a reduction in smoking.

The study presented here demonstrated that the combination of a comprehensive healthy lifestyles/smoking cessation intervention delivered by trained mental health staff can, in conjunction with varenicline, produce smoking abstinence rates of 36% at 3-months (whilst still on varenicline) and 42% three months later, having ceased the medication. This is higher than we reported in our studies with similar patients, using an identical intervention but with NRT (abstinence rate 19%). Furthermore, despite this being a psychiatrically high risk group, only one participant dropped out because of worsening psychiatric symptoms, albeit that it was not clear whether these were directly exacerbated by the varenicline. The findings regarding psychiatric adverse events are compatible with those reported by McClure et al [34] in patients with depression. Indeed, overall in our study, the side effect profile was similar to those experienced by people without a mental illness, who cease smoking. Two patients ceased the medication because of nausea and resumed smoking at baseline rates; one further patient in our study dropped out because of constipation, but recommenced varenicline as he feared starting smoking again. It is also worth noting that smoking cessation has also been associated with depression, notably in people with a past history of depression [38].

There are a number limitations to this study, notably the small number of participants and the fact that we did not control for multiple testing on outcome measures. The heterogeneity of diagnoses is also a drawback, albeit it allowed a more ‘real life’ clinical sample than would be usual in randomised controlled trials. We did not include a control group, but could make some comparisons with the outcomes from previous studies using NRT, as the participant sample was similar and the non-pharmacological intervention was manualised and has high fidelity. Of course, randomised controlled comparison trials will more definitively determine the superiority or otherwise on varenicline vs. NRT in this patient group. Also, longer-term outcome studies are required to determine relapse rates and guide duration of therapy. Furthermore, measures of the effects of varenicline on neurobiological markers and cognitive functioning would usefully be included in such longer-term studies, in order to understand better the underlying neurobiological mechanisms that drive so many people with schizophrenia, to smoke. A recent randomised placebo-controlled trial [39], for example, showed varenicline to be associated with reduced sensory P50 gating, startle reactivity and antisaccade errors in people with schizophrenia.

At this stage, we believe it is reasonable to conclude that varenicline can be effective in reducing smoking in people with severe mental illness, in conjunction with a comprehensive psychosocial intervention. We also conclude that most side effects are tolerable and are similar to those experienced by people without a mental illness. However, due to the potential for worsening of psychiatric symptoms in such high risk patients, we suggest that varenicline is used in such patients only with careful and comprehensive mental state monitoring, expressly for depressive symptoms and suicidality. Whilst the results of the current open study are encouraging, replication in an adequately powered randomised controlled trial is required before definitive conclusions can be drawn.
REFERENCES:


[18] Jorenby DE, Hays JT, Rigotti NA. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomised controlled trial. JAMA 2006; 296: 56-63


[22] Kuehn BM. FDA warns of adverse events linked to smoking cessation drug and antiepileptics. JAMA 2008; 299: 1121-1122


[38] Covey LS, Glassman AH, Stetner F. Major depression following smoking cessation. Am J Psychiatry 1997; 154: 263-265

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Diagnoses</th>
<th>Cigs at Entry</th>
<th>Cigs at 3 mths</th>
<th>Cigs at 6 mths</th>
<th>Main reported Side Effects</th>
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<td>Mood disorder with psychosis</td>
<td>20</td>
<td>5</td>
<td>10</td>
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<td>0</td>
<td>0</td>
<td>Insomnia, vivid dreams, increased appetite</td>
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<td>40</td>
<td>20</td>
<td>20</td>
<td>Blurred vision, dry mouth, fatigue, thirst, dizziness, nausea</td>
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<td>0</td>
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<td>12</td>
<td>40</td>
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<td>7</td>
<td>6</td>
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<td>7</td>
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<td>0</td>
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<td>-</td>
<td>-</td>
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<td>25</td>
<td>2</td>
<td>0</td>
<td>Dry mouth, thirst</td>
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Table 2: Baseline and post-treatment (six month) ratings
Cigs: cigarettes; CO: carbon dioxide; ppm: parts per million; FTND Fagerstrom Test for Nicotine Dependence

<table>
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<tr>
<th>Measure</th>
<th>Before treatment</th>
<th>After treatment (6month follow-up)</th>
<th>Difference</th>
<th>95% CI of the difference</th>
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<td>M</td>
<td>SD</td>
<td>Range</td>
<td>M</td>
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<td>15 - 40</td>
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<td>9.29</td>
<td>15 - 40</td>
<td>18.89</td>
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<td>30.08</td>
<td>19.25</td>
<td>10 – 77</td>
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<td>1.91</td>
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<td>.39</td>
<td>.25 – 1.75</td>
<td>.87</td>
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<td>Withdrawal (self-rated)</td>
<td>1.29</td>
<td>.58</td>
<td>0 – 2.33</td>
<td>.96</td>
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</tbody>
</table>

Table 2: Baseline and post-treatment (six month) ratings
Cigs: cigarettes; CO: carbon dioxide; ppm: parts per million; FTND Fagerstrom Test for Nicotine Dependence