ADDICTION
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COMMENTARY

# Commentary on Roberts *et al.* (2016): Bupropion and varenicline are efficacious and well-tolerated cessation medications for smokers with serious mental illness

*This network meta-analysis concluded that bupropion and varenicline are efficacious and well-tolerated cessation medications for smokers with serious mental illness who are stably treated and motivated to quit. Poorly graded data quality point to the need for direct comparisons of cessation medications, including nicotine replacement, in larger psychiatric samples.*

Varenicline, bupropion and nicotine replacement therapy (NRT) improve success with quitting smoking [1]. A network meta-analysis conducted with studies of non-psychiatric samples of smokers indicated equal efficacy for bupropion and single forms of NRT and superior efficacy for varenicline and combination NRT [2]. Unknown is the relative efficacy and tolerability of cessation medications among people with serious mental illness (SMI), a group with elevated smoking prevalence and increased risk for tobacco-related harms [3].

Roberts *et al.*'s network meta-analysis sought to address this gap [4]. The authors defined SMI as any non-organic disorder with psychotic features that results in substantial disability. Of the 14 randomized controlled trials (RCTs) included, 11 were conducted with smokers with schizophrenia or schizoaffective disorder and three with smokers with bipolar disorder, two of which enrolled only five participants, more akin to case reports than clinical trials. Excluded were samples of smokers with unipolar depression, post-traumatic stress disorder (PTSD), other anxiety disorders and non-nicotine substance use disorders. Participants were recruited from the community, screened as stably treated, medication adherent and motivated to quit.

Nine of the 14 trials, with 356 total participants, reported on abstinence outcomes, and 10 trials with 423 participants reported on tolerability (defined as trial discontinuation due to any adverse event). This averaged to about 40 participants per trial or about 20 per treatment group; retention rates were unreported. Although most of the individual trials were underpowered, the synthesized findings indicated statistically significant treatment effects with wide credibility intervals (CrI), for both bupropion [odds ratio (OR) = 4.51, 95% CrI = 1.45, 14.04] and varenicline (OR = 5.17, 95% CrI = 1.78, 15.06). Treatment efficacy for the two medications was comparable (OR = 1.15, 95% CrI = 0.24, 5.45), with no significant difference in tolerability for the two active drugs relative to placebo.

Roberts *et al.* rated the evidence as very low quality [4], and with few studies there were no closed loops within their network. In a closed loop, each indirect source of evidence is complemented by a direct source of evidence for the same comparison. There were five bupropion-placebo trials and three varenicline-placebo trials; only one study had a direct comparison of varenicline and bupropion, and with five completers per group, abstinence outcomes were not reported [5]. No trial tested NRT relative to placebo. Research with smokers with SMI is relatively recent in the tobacco control field (i.e. all trials were published post-2000), whereas most placebo-controlled trials of NRT were conducted in the mid- to late-1990s. A comparison of NRT with bupropion versus NRT with placebo in two trials had a large effect (OR = 4.13) with a wide credibility index (95% CrI = 0.92, 18.57) that was not statistically significant.

On the horizon, a large RCT was completed recently to address several gaps in the treatment literature [6]. Publication of study findings is anticipated in 2016. The trial had direct comparisons, both for safety and efficacy, of bupropion, varenicline and NRT patch, and enrolled more than 4000 smokers with mental illness, including schizophrenia and bipolar disorder. A safety trial requested by regulators, the study will inform the US Food and Drug Association's (FDA) neuropsychiatric-related box warnings for bupropion and varenicline added in 2009 following post-marketing surveillance adverse event reports [7]. The extent to which Roberts *et al.*'s network meta-analysis is in line with findings from this large RCT will be interesting both empirically and clinically.

Limited to motivated-to-quit smokers with SMI, Roberts *et al.*'s conclusions are consistent with broader tobacco treatment/mental illness literature. Two recent trials on acute in-patient psychiatry units recruited smokers with varied diagnoses, varying in readiness to quit [8,9]. Relative to placebo, the stage-tailored cessation intervention combined with NRT resulted in a twofold greater abstinence and without adverse effects on mental health recovery. Two RCTs of cessation treatment integrated within psychiatric care for PTSD compared to smoking cessation referral yielded two- to fivefold increases in abstinence and without harm to symptom abatement [10,11]. All FDA-approved cessation medications were available to smokers in both conditions; the number of counseling sessions received and days of cessation medication used explained more than a third of the treatment effect. All 14 trials in Roberts *et al.*'s meta-analysis included weekly counseling (from nine to 15+ visits) that encouraged and supported

cessation medication adherence. The conclusion that bupropion and varenicline are efficacious medications for smokers with SMI is an important clinical finding, and worth emphasizing is the utility of ongoing behavioral counseling to support patients' efforts throughout the quit attempt.

Individuals with SMI want to quit and can quit with evidence-based cessation medications and counseling support. The network meta-analysis by Roberts *et al.* [4] lacked an NRT comparator and found similar efficacy for bupropion and varenicline. As more published trials become available on smokers with mental illness, it will be of interest to see how the evidence further unfolds.

## Declaration of interests

Judith Prochaska has consulted to Pfizer, which makes smoking cessation medications, and has been an expert witness for plaintiffs counsel in court cases against the tobacco companies.

**Keywords** Meta-analysis, psychiatry, serious mental illness, smoking, systematic review, tobacco.

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