Dr Salvadore and Colleagues Reply

To the Editor: We thank Dr Rybakowski and colleagues for their comments on our article, and for raising the potentially interesting link between the cholinergic system and mood disorders.

We agree that the cholinergic system is likely to play a pivotal role in the pathophysiology and treatment of mood disorders (including both unipolar and bipolar disorders in equal measure). However, it is our opinion that the evidence supporting a "cholinergic theory" for the switch process per se is, at best, unclear. Much of the currently available evidence is anecdotal and unsubstantiated by well-designed studies.

As Rybakowski and colleagues note in their letter, the contrasting effects of anticholinergic and cholinomimetic agents in determining mood elevation and mood depression, respectively, have long been hypothesized.[1] Indeed, well before the psychopharmacologic era, extracts from plants containing anticholinergic alkaloids (eg, *Atropa belladonna*) were widely used for their sedative and antidepressant properties in patients with psychiatric disorders.[2]

However, it was not until recently that the antidepressant efficacy of drugs capable of specifically modulating the cholinergic system—rather than multiple neurotransmitter systems as occurs with tricyclic antidepressants (TCAs)—was empirically tested in randomized, controlled studies of patients with mood disorders. As Rybakowski and colleagues correctly note, there is compelling evidence from such studies to suggest that the cholinergic system plays a major role in treatment response and in the pathophysiology of depression. However, the evidence regarding the involvement of the cholinergic system in the switch process is considerably less straightforward.

In the first study[3] investigating the antidepressant efficacy of the antimuscarinic drug scopolamine, 9 patients with bipolar disorder and 9 patients with unipolar depression completed the study; change in Montgomery-Asberg Depression Rating Scale scores after scopolamine was similar in unipolar and bipolar depressed patients. Notably, scopolamine administration was not associated with manic/hypomanic switches or with a significant increase in Young Mania Rating Scale scores in patients with bipolar disorder; euphoria was reported by 1 patient after receiving scopolamine and by 1 patient after receiving placebo.

In the replication study,[4] enrollment was limited to patients with unipolar depression, making it impossible to draw any conclusions pertaining to bipolar disorder; no patient experienced euphoria after receiving either scopolamine or placebo. It is important to note that neither study could be considered to provide conclusive evidence, as the primary aim of both studies was to investigate the antidepressant efficacy of scopolamine, not to draw inferences about its mood-elevating properties; the original study[3] was also clearly underpowered to detect such an effect.

Rybakowski and colleagues propose that anticholinergic mechanisms may cause the switch process, drawing evidence (1) from a rodent study[5] conducted 30 years ago that showed antidepressant-like activity associated with scopolamine and (2) from studies[6,7] that noted central cholinergic receptor hyperactivity in mood disorders. They also mention that TCAs are associated with increased risk for switch compared to non-TCAs and that, among TCAs, switches are more frequently associated with drugs that cause higher muscarinic receptor blockage (eg, amitriptyline) rather than those with low muscarinic affinity (eg, desipramine).

With regard to the first point, there is presently no well-validated animal model of the switch process and, concomitantly, no evidence suggesting that antidepressant-like activity observed with any compound in animal models of depression represents a valid animal model of the switch process. As regards the second point, supersensitivity of the cholinergic system does not imply a direct link with switch. Indeed, the investigator who described this phenomenon described it as pertaining to mood disorders in general, not the switch process in particular.[6] Finally, and perhaps most significantly, no controlled data exist suggesting that antidepressants with greater cholinergic receptor affinity are more likely to produce switch.

The crux of the argument by Rybakowski and colleagues centers on their retrospective chart review,[8] which found a higher rate of switch in patients with bipolar disorder treated with TCAs versus non-TCAs. In addition to the obvious limitation that theirs was not a controlled prospective study, it is our contention that switches occurring in patients receiving TCAs do not necessarily imply that the cause of this association was their anticholinergic properties. Several factors could explain this association, most notably a different affinity to serotonergic and noradrenergic transporters and receptors.[9]

Finally, Rybakowski and colleagues argue that "a meaningful role of anticholinergic mechanisms operating in antidepressant activity, and *consequently* in switch processes, deserves to be strongly mentioned" and that, furthermore, "there is a *clear relationship* between the mechanisms of the switch process and antidepressant activity and efficacy" to support the link between a given drug's antidepressant efficacy and its switch-inducing potential (emphasis ours). We respectfully but strongly disagree with this point. In our opinion, this link is not supported by empirical evidence, which actually suggests that different antidepressant mechanisms with similar clinical efficacy differ in their risk of inducing mood elevation (reviewed in Salvadore et al[10]). This equivalence is also not supported by clinical data from the National Institute of Mental Health studies,[3,4] which showed that the effect sizes for scopolamine's antidepressant effects were larger than with conventional antidepressants and not accompanied by an increased propensity to experience mood switching.

In conclusion, we believe that until controlled data become available showing that mood switches occur more commonly with anticholinergic compounds (eg, scopolamine) than with noncholinergic drugs in bipolar depression, the claim that anticholinergic mechanisms may be "a forgotten cause of the switch process" remains speculative and premature.

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