In the replication study, 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 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 conducted 30 years ago that showed antidepressant-like activity associated with scopolamine and (2) from studies 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. 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, 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.

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). This equivalence is also not supported by clinical data from the National Institute of Mental Health studies, which showed that the effect sizes for scopolamine's antidepressant effects were larger with 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.

References


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