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Review

The selegiline transdermal system in major depressive disorder: A systematic review of safety and tolerability ☆

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Abstract

Background: Monoamine oxidase inhibitors (MAOIs) are highly efficacious antidepressants, but safety concerns have limited their broad use.
Methods: We reviewed key safety and tolerability data from all clinical trials of patients with major depressive disorder (MDD) accrued during the clinical development of the selegiline transdermal system (STS), as reported to the Food and Drug Administration. This review includes data from both controlled and uncontrolled clinical trials involving STS-treated ($n=2036$) and placebo-treated ($n=668$) patients.
Results: Except for the initial trial, subsequent trials, which involved STS doses ranging from 3 mg/24 h to 12 mg/24 h, lacked tyramine restrictions, and no acute hypertensive reactions occurred during study treatment. Safety experience with STS 6 mg/24 h supports this therapeutic dose without tyramine dietary modifications, but until more data are available for STS doses 9 mg/24 h and 12 mg/24 h, foods that are rich sources of tyramine should be avoided. The principal side effects of STS therapy were local dermal reactions and insomnia, both of which were dose-related. Side effects associated with MAOI treatment, such as sexual dysfunction and excessive weight gain, were uncommon.
Conclusions: A comprehensive review of safety from the clinical development program suggests that the STS is safe and well tolerated, with an improved safety margin compared with orally administered MAOIs.

Keywords: Major depressive disorder; Selegiline transdermal system; Tyramine; Antidepressants; Monoamine oxidase inhibitors; Safety

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Contents

1. Introduction

Monoamine oxidase inhibitors (MAOIs), the first class of effective antidepressant drugs, have been extensively investigated since their introduction in the 1950s (Amsterdam and Chopra, 2001; Robinson, 2002). Although MAOIs enjoyed a reputation for robust efficacy in treating major depressive disorder (MDD), enthusiasm for their use has been tempered by the risk of tyramine-induced acute hypertensive reactions and the consequent need for tyramine dietary restrictions (Blackwell, 1963). Therefore, therapy with oral MAOIs is largely relegated to patients with MDD with atypical features or to patients with treatment-resistant depression.

Despite the advent of the tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs), more than 30% of patients with MDD will not achieve full remission even after a series of antidepressant treatments. Because of this disappointing response rate, it is important to continue searching for novel, more effective antidepressants (Greden, 2002). Attempts to improve the safety of MAOIs have involved developing selective irreversible and reversible MAOIs that might obviate the need for tyramine dietary restrictions. While irreversible, selective monoamine oxidase type A (MAO-A) inhibitors, like clorgyline, have been shown to be effective antidepressants, they still require avoidance of tyramine-rich foods (Rudorfer, 1992). Reversible MAO-A inhibitors, like moclobemide and brofaromine, have improved safety profiles with modest increases in tyramine sensitivity but inferior efficacy compared with conventional MAOIs (Amsterdam and Chopra, 2001; Robinson, 2002).

Selegiline, an irreversible inhibitor with selectivity for monoamine oxidase type B (MAO-B) at low oral doses, has an established safety and efficacy profile as adjunctive treatment of Parkinson's disease (PD). At therapeutic doses up to 10 mg/day orally for PD, selegiline can be safely administered without the need for a tyramine-restricted diet. Oral selegiline may be an effective antidepressant (McGrath et al., 1989; Mann et al., 1989) at doses in excess of 20 mg daily when enzyme selectivity is lost (MAO-A is inhibited in addition to MAO-B), thus necessitating tyramine dietary restrictions (Prasad et al., 1988; Sunderland et al., 1994).

A transdermal formulation of selegiline recently approved for treatment of MDD provides greater systemic delivery of selegiline to the brain with relative sparing of gastrointestinal MAO-A enzyme (Mawhinney et al., 2003; Wecker et al., 2003). The selegiline transdermal system (STS) achieves antidepressant concentrations of selegiline in neuronal tissues with fewer effects on gastrointestinal MAO-A, the principal enzymatic barrier to ingested tyramine. A series of clinical pharmacology studies in healthy subjects delineated the limited effects on tyramine sensitivity of STS compared with oral MAOI antidepressants (Azzaro et al., 2006a).

Therapeutic benefits of STS for treatment of MDD have been documented in both short-term (Bodkin and Amsterdam, 2002; Amsterdam, 2003; Feiger et al., 2006) and long-term, placebo-controlled trials (Amsterdam and Bodkin, 2006). In this review, we summarize available