ABSTRACT

Purpose: Tapentadol extended-release (ER) oral tablets prescribing information warns there have been reports of serotonin syndrome with concurrent use of tapentadol and serotonergic drugs. We analyzed pooled safety data from 11 randomized, double-blind, placebo-controlled trials to identify other potential pharmacodynamic drug interactions associated with concomitant use of tapentadol and a selective serotonin reuptake inhibitor (SSRI) or serotonin norepinephrine reuptake inhibitor (SNRI).

Methods: Safety populations were pooled from 7 studies investigating oral immediate-release tapentadol vs placebo over 3 to 10 days for acute pain and 4 studies of tapentadol ER vs placebo over 15 weeks for chronic pain. All 11 studies permitted SSRIs if dose was stable at baseline and during study. SNRIs were prohibited, but some subjects deviated from protocol and took an SNRI. Across studies, 3,269 subjects received tapentadol 1,501 received placebo. Advence event (AE) incidences were compared for tapentadol vs placebo using safety data from only subjects who took an SSRI (n = 310), SNRI (n = 31), or both (n = 4). Thus, all subjects analyzed (N = 345) were taking fluoxetine, paroxetine, fluvoxamine, sertraline, citalopram, eszopiclone, venlafaxine, or duloxetine at baseline. Since SSRIs/SNRIs have an established AE profile, this analysis enabled comparison of AEs reported for tapentadol + SSRI/SNRI (n = 208) vs placebo + SSRI/SNRI (n = 137) to assess if adding tapentadol vs adding placebo to SSRI or SNRI therapy changed the profile.

Results: Incidences of nausea, vomiting, dry mouth, dizziness, somnolence, pruritus, hyperhidrosis, and hot flush were significantly higher (P<0.05) for tapentadol + SSRI/SNRI vs placebo + SSRI/SNRI, but were similar to incidences listed in tapentadol labeling. Other AEs occurred at numerically higher rates for tapentadol + SSRI/SNRI vs placebo + SSRI/SNRI, but most were also expected for tapentadol alone. Unexpected AEs with rates >2% for tapentadol + SSRI/SNRI were pharyngodyingostritis pain (P=0.045), abdominal pain (ns), and myalgia (ns).

Conclusion: This post hoc analysis of pooled clinical trial data did not identify new clinically relevant adverse drug interactions associated with adding tapentadol to SSRI/SNRI therapy.

INTRODUCTION

• Tapentadol is a centrally acting synthetic analgesic. Preclinical studies have shown tapentadol is a μ-opioid receptor agonist and norepinephrine reuptake inhibitor, and analgesia in animal models is derived from both properties.

• There have been reports of serotonin syndrome with concurrent use of tapentadol and serotonergic drugs.

PURPOSE

• Pooled safety data from 11 randomized, double-blind, placebo-controlled trials were analyzed post hoc to identify potential pharmacodynamic drug-drug interactions associated with concomitant use of tapentadol and a selective serotonin reuptake inhibitor (SSRI) or a serotonin norepinephrine reuptake inhibitor (SNRI).

• Safety populations were pooled from eleven Phase 3 clinical trials of immediate-release (IR) and extended-release (ER) oral tablet formulations of tapentadol (Table 1).

• Seven studies investigated the efficacy and safety of tapentadol IR in acute pain models. Four studies investigated the efficacy and safety of tapentadol ER in chronic pain models.

• All 11 trials were prospective, multicenter, randomized, parallel-group, double-blind, and placebo-controlled.

• Ten studies employed an active control (ie, oxycodone or morphine) to verify the sensitivity of the pain model.

• Eight studies permitted concomitant SSRI use if the subject was taking a stable (unchanged) dose for ≥3 months prior to screening. Three studies permitted concomitant SNRI use if the subject was taking a stable (unchanged) dose for ≥3 months prior to screening.

• All 11 study protocols prohibited the use of SNRIs within 2 weeks before screening and throughout the double-blind treatment period because SNRIs might confound assessments of analgesic efficacy.

• One study was terminated prematurely due to slow recruitment and high rate of discontinuation. Another study was terminated prematurely due to slow enrollment.

METHODS

• In this post hoc analysis of pooled safety data, the incidence rates of treatment-emergent adverse events (TEAEs) were compared for tapentadol versus placebo using safety data from only subjects who were taking an SSRI or SNRI at baseline. Subjects were excluded from the analysis if they were not taking one of the SSRIs or SNRIs listed in Table 2 at baseline.

• The design of this analysis (Figure 1) enabled comparison of adverse events (AEs) reported for tapentadol + SSRI/SNRI versus placebo + SSRI/SNRI to assess the safety of adding tapentadol (vs adding placebo) to ongoing SSRI or SNRI therapy and thereby identify potential pharmacodynamic drug interactions. By comparing the subgroups taking an SSRI or SNRI at baseline (green boxes), the benefit of randomization is maintained for a statistical comparison.
Post Hoc Analysis of Pooled Safety Data From Eleven Phase 3 Clinical Trials to Identify Potential Pharmacodynamic Drug Interactions Between Tapentadol and SSRIs/SNRIs

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RESULTS

Among 218 subjects in the tapentadol + SSRI/SNRI group (Table 1), 190 reported taking 1 SSRI, 3 reported taking 2 different SSRIs, 14 reported taking 1 SNRI, and 2 reported taking both an SSRI and an SNRI during the trial (Table 2)

Among 137 subjects in the placebo + SSRI/SNRI group (Table 1), 117 reported taking 1 SSRI, 10 reported taking 1 SNRI, and 2 reported taking both an SSRI and an SNRI during the trial (Table 2)

Indicences of nausea, vomiting, dry mouth, dizziness, somnolence, pruritus, hyperhidrosis, hot flush, and pharyngolaryngeal pain were significantly higher (P<0.05) for tapentadol + SSRI/SNRI versus placebo + SSRI/SNRI (Table 3)

Indicences of constipation, anxiety, insomnia, lethargy, abnormal dreams, abdominal pain, tremor, myalgia, depression, and arthralgia were numerically higher for tapentadol + SSRI/SNRI versus placebo + SSRI/SNRI, but the difference in incidence was not statistically significant (Table 3)

DISCUSSION

Most of the AEs listed in Table 3 for tapentadol are qualitatively and quantitatively similar to the AEs listed in the tapentadol IR and/or tapentadol ER labeling

Unexpected AEs (ie, defined as AEs not listed in the product labeling) with incidence >2% for tapentadol + SSRI/SNRI included pharyngolaryngeal pain (P=0.045 vs placebo), abdominal pain (not statistically significant vs placebo), and myalgia (not statistically significant vs placebo)

Limitations to this post hoc analysis include the relatively small subpopulation of patients taking baseline SSRI or SNRI (N=345) and disparity across study designs such as different treatment durations (from 3 days to 15 weeks), pain models (acute vs chronic), clinical settings (inpatient vs outpatient), dosage forms (IR vs ER), dosage regimens (fixed vs flexible), and mean age (ie, younger in postoperative pain studies vs chronic pain studies)

The tapentadol + SSRI/SNRI subgroup consisted of all subjects who received any dosage regimen of tapentadol, thereby precluding the ability to detect possible dose or formulation effect on pharmacodynamic drug interaction. Likewise, the effect of a specific SSRI or SNRI drug or their dosages was not evaluated

Potential confounding by SNRI-induced noradrenergic effects was not evaluated

There were too few subjects taking tapentadol to make statistical comparisons of the AE profiles for tapentadol + SSRI/SNRI versus placebo + SSRI/SNRI (n=13) or oxycodone/morphine + SSRI/SNRI (n=15)

Statistical comparisons of tapentadol versus oxycodone or morphine were not performed because these μ-opioid agonist agents served as active controls to verify the sensitivity of the pain models studied in the clinical trials and it was thought that comparison of tapentadol + SSRI/SNRI versus oxycodone/morphine + SSRI/SNRI would not contribute appreciably to identifying potential pharmacodynamic drug interactions between tapentadol and SSRIs or SNRIs

CONCLUSIONS

This post hoc analysis of pooled safety data from 11 randomized Phase 3 clinical trials did not identify new clinically relevant adverse drug interactions associated with adding tapentadol to SSRI or SNRI therapy. No conclusions can be made about the concomitant use of tapentadol with >1 serotonergic agent