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Post Hoc Analysis of Pooled Safety Data From Eleven Phase 3 Clinical Trials to Identify Potential Pharmacodynamic Drug Interactions Between Tapentadol and SSRIs/SNRIs

Vincent Brett, MS, PharmD; Christopher Sikes, PharmD; Jim Xiang, PhD; Charles Oh, MD; David Biondi, DO
Janssen Scientific Affairs, LLC, Raritan, NJ, USA.

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; 1,901 received placebo. Adverse event (AE) incidences were compared for tapentadol vs placebo using 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, escitalopram, 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 pharyngolaryngeal 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

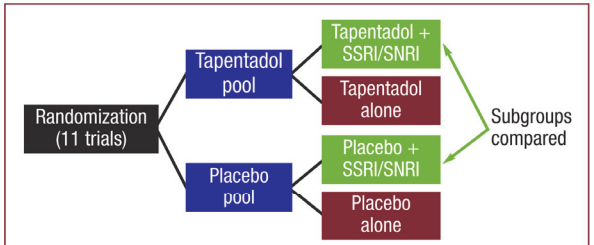
- Tapentadol is a centrally acting synthetic analgesic. Preclinical studies have shown tapentadol is a μ-opioid receptor agonist and norepinephrine reuptake inhibitor, and analgesia in animal models is derived from both properties[1]
- There have been reports of serotonin syndrome with concurrent use of tapentadol and serotonergic drugs[2]

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)

METHODS

- 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.[3-9] Four studies investigated the efficacy and safety of tapentadol ER in chronic pain models[10-13]
  - All 11 trials were prospective, multicenter, randomized, parallel-group, double-blind, and placebo-controlled[3-13]
  - Ten studies employed an active control (ie, oxycodone or morphine) to verify the sensitivity of the pain model.[3-12] One study employed a randomized-withdrawal, clinical trial design and, therefore, did not have an active control group[13]
  - Eight studies permitted concomitant SSRI use if the subject was taking a stable (unchanged) dose for ≥1 month prior to screening.[3-9,13] Three studies permitted concomitant SSRI use if the subject was taking a stable (unchanged) dose for ≥3 months prior to screening[10-12]
  - 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.[3-13] However, some subjects had deviated from protocol and took an SNRI
  - One study was terminated prematurely due to slow recruitment and high rate of discontinuation.[7] Another study was terminated prematurely due to slow enrollment[8]
- Safety populations were defined as all randomized patients who took ≥1 dose of study medication
- 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



TEAE, treatment-emergent adverse event; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor.

Figure 1. Statistical analysis: incidence rates of TEAEs for tapentadol + SSRI/SNRI versus placebo + SSRI/SNRI were compared using a two-tail Fisher exact test.

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DATA ANALYSIS

Table 1. Brief Description of Eleven Phase 3 Tapentadol Trials, Subject Disposition, Safety Population, and Distribution of SSRI/SNRI Usage

Pain Model	Trial Design and Setting	Randomization Ratio	No. (n) of Subjects Randomized and Randomized Treatment Groups	Dosing Interval and Duration of DB Period	Age (y), Mean ± SD (Range)	No. (n) of Subjects in DB Safety Population				No. (n) of Subjects Who Took SSRI and/or SNRI During Trial		
						PBO	TAP	OXY or MS	Total	PBO	TAP	OXY or MS
Postoperative bunionectomy[3]	R, DB, PC, AC, PG, MC, inpatient, fixed-dose	1:1:1:1:1	n = 119 tapentadol IR 50 mg n = 120 tapentadol IR 75 mg n = 118 tapentadol IR 100 mg n = 125 oxycodone IR 15 mg n = 121 placebo N = 603 total	q4-6h x 3 days	44.3 ± 13.66 (18-77)	120	357	125	602	8	21	9
Postoperative bunionectomy[4]	R, DB, PC, AC, PG, MC, inpatient, fixed-dose	4:4:4:1	n = 275 tapentadol IR 50 mg n = 278 tapentadol IR 75 mg n = 279 oxycodone IR 10 mg n = 69 placebo N = 901 total	q4-6h x 3 days	43.1 ± 13.05 (18-78)	69	553	279	901	0	35	17
Postoperative bunionectomy[5]	R, DB, PC, AC, PG, MC, inpatient, fixed-dose	1:1:1	n = 96 tapentadol IR 75 mg n = 96 morphine sulfate IR 30 mg n = 99 placebo N = 291 total	q4-6h x 3 days	44.0 ± 13.55 (18-78)	99	96	96	291	9	3	1
Postoperative abdominal hysterectomy[6]	R, DB, PC, AC, PG, MC, inpatient, fixed-dose	1:1:1:1:1	n = 168 tapentadol IR 50 mg n = 171 tapentadol IR 75 mg n = 176 tapentadol IR 100 mg n = 170 morphine sulfate IR 20 mg n = 169 placebo N = 854 total	q4-6h x 3 days	47.5 ± 6.03 (29-87)	169	515	170	854	0	1	1
Postoperative total hip replacement[7]	R, DB, PC, AC, PG, MC, inpatient, fixed-dose	1:1:1:1:1	n = 77 tapentadol IR 50 mg n = 71 tapentadol IR 75 mg n = 75 tapentadol IR 100 mg n = 67 oxycodone IR 10 mg n = 75 placebo N = 365 total	q4-6h x 3 days	62.7 ± 11.11 (20-84)	68	202	60	330	7	21	4
Vertebral compression fracture[8]	R, DB, PC, AC, PG, MC, outpatient, flexible dose	2:2:1	n = 44 tapentadol IR 50-75 mg n = 43 oxycodone IR 5-10 mg n = 21 placebo N = 108 total	q4-6h as needed x 10 days	69.5 ± 12.58 (21-91)	21	44	43	108	3	6	3
End-stage degenerative joint disease[9]	R, DB, PC, AC, PG, MC, outpatient, fixed-dose	1:1:1:1	n = 157 tapentadol IR 50 mg n = 168 tapentadol IR 75 mg n = 172 oxycodone IR 10 mg n = 169 placebo N = 666 total	q4-6h x 10 days	61.2 ± 9.83 (20-79)	169	325	172	666	15	29	14
Osteoarthritis of knee[10]	R, DB, PC, AC, PG, MC, outpatient, flexible dose	1:1:1	n = 346 tapentadol ER 100-250 mg n = 345 oxycodone CR 20-50 mg n = 339 placebo N = 1,030 total	Twice daily x 15 weeks	58.3 ± 9.85 (40-91)	337	344	342	1,023	30	28	22
Osteoarthritis of knee[11]	R, DB, PC, AC, PG, MC, outpatient, flexible dose	1:1:1	n = 320 tapentadol ER 100-250 mg n = 333 oxycodone CR 20-50 mg n = 337 placebo N = 990 total	Twice daily x 15 weeks	62.1 ± 9.26 (18-89)	337	319	331	987	9	6	8
Chronic low back pain[12]	R, DB, PC, AC, PG, MC, outpatient, flexible dose	1:1:1	n = 321 tapentadol ER 100-250 mg n = 334 oxycodone CR 20-50 mg n = 326 placebo N = 981 total	Twice daily x 15 weeks	49.9 ± 13.83 (40-87)	337	318	328	965	44	37	29
Diabetic peripheral neuropathy[13]	Randomized-withdrawal, DB, PC, PG, MC, outpatient, flexible dose	1:1	n = 199 tapentadol ER 100-250 mg n = 196 placebo N = 395 total	Twice daily x 12 weeks	60.2 ± 10.62 (29-87)	193	196	0	389	12	21	[a]
					Total	1,901	3,269	1,946	7,116	137	208	108

SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor; DB, double-blind; SD, standard deviation; PBO, placebo; TAP, tapentadol; OXY, oxycodone hydrochloride; MS, morphine sulfate; R, randomized; PC, placebo-controlled; AC, active-controlled; PG, parallel group; MC, multicenter; IR, immediate release; ER, extended release; CR, controlled release.
[a]Study did not include an active control group.

Table 2. SSRIs and SNRIs Used During 11 Trials[a]

	Placebo (n = 137), n	Tapentadol (n = 208), n
Sertraline	28	48
Escitalopram	27	43
Fluoxetine	26	39
Citalopram	19	36
Paroxetine	17	30
Fluvoxamine	2	2
Duloxetine	14	8
Venlafaxine	6	7
Total SSRI/SNRI[b]	139	213

SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor.
[a]No patients received desvenlafaxine or milnacipran because these SNRIs were investigational drugs at the time most tapentadol trials were being conducted.
[b]Three subjects switched from their baseline SSRI to a different SSRI sometime during the trial. Four subjects switched between an SSRI and an SNRI during the trial.

Table 3. TEAEs That Occurred at an Incidence Rate ≥2% in Subjects Taking Concomitant Tapentadol + SSRI/SNRI, Based on Post Hoc Analysis of 11 Pooled Randomized, Placebo-Controlled Phase 3 Trials

Preferred Term	Placebo + SSRI/SNRI (n = 137), %	Tapentadol + SSRI/SNRI (n = 208), %
Any AE	64.2	75.5
Nausea	10.2	21.2[a]
Dizziness	7.3	20.2[a]
Somnolence	4.4	12.5[a]
Headache	14.6	12.0
Vomiting	2.9	8.7[a]
Dry mouth	1.5	8.2[a]
Constipation	3.6	7.7
Pruritus	1.5	6.7[a]
Hyperhidrosis	0.7	5.8[a]
Anxiety	0.7	4.8
Hot flush	0	4.3[a]
Insomnia	2.2	4.3
Fatigue	4.4	4.3
Pharyngolaryngeal pain	0	3.4[a]
Lethargy	0	2.9
Pyrexia	3.6	2.9
Diarrhea	4.4	2.9
Abnormal dreams	0	2.4
Abdominal pain	0.7	2.4
Tremor	0.7	2.4
Myalgia	1.5	2.4
Depression	1.5	2.4
Arthralgia	2.2	2.4

TEAE, treatment-emergent adverse event; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor; AE, adverse event.
[a]P <0.05 vs placebo.

RESULTS

- Among 208 subjects in the tapentadol + SSRI/SNRI group (**Table 1**), 190 reported taking 1 SSRI, 3 reported taking 2 different SSRIs, 13 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, 18 reported taking 1 SNRI, and 2 reported taking both an SSRI and an SNRI during the trial (**Table 2**)
- Incidences 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**)
- Incidences 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[1,2]
- 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 SNRIs to make statistical comparisons of the AE profiles for tapentadol + SNRI (n = 20) versus placebo + 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**