PND8

PATIENT SELF-ASSESSMENTS IN ADVANCED PARKINSON'S DISEASE WITHIN UPDRS AND "OFF" TIME SUBGROUPS: COMPARISON OF IPX066 WITH IMMEDIATE-RELEASE CARBIDOPA-LEVODOPA

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OBJECTIVES: IPX066, an extended-release capsule formulation of carbidopa-levodopa (CD-LD), is designed to produce a rapid increase in plasma levodopa concentrations similar to immediate-release CD-LD (IR), but with sustained plasma levels allowing dosing every 6 hours. This post hoc analysis investigated whether baseline Parkinson's disease (PD) severity influenced the patient reported efficacy of IPX066 vs. IR in advanced PD patients. **METHODS:** IPX066 was evaluated in a randomized, double-blind, Phase 3 study vs. IR CD-LD for 13 weeks (N=393). Patients were split into subgroups of higher and lower disease severity based on median baseline "off" time (5.67 hr) and Unified Parkinson's Disease Rating Scale (UPDRS) Parts II+III (score: 32). Patient Global Impression (PGI), and the change from baseline in "off" time and "on" time with troublesome dyskinesia by PD diary were analyzed for each subgroup. **RESULTS:** IPX066 significantly improved PGI (P<.0001) and "off" time (P<.0001) compared with IR CD-LD in the overall randomized population. IPX066 significantly improved PGI scores compared with IR CD-LD in both higher severity subgroups (P<.001) and lower severity subgroups (P<.02). Numerical improvements from baseline in "off" time were seen with IPX066 vs. IR CD-LD in each disease severity subgroup. The improvements in "off" time were significantly greater for IPX066 vs. IR CD-LD in the higher severity "off" (P<.0001) and in both the higher (P=.02) and lower severity (P=.0001) UPDRS subgroups. The improvement by IPX066 compared to IR CD-LD in the lower severity "off" subgroup did not reach significance (P=.11), possibly due to a floor effect. IPX066 did not significantly worsen "on" time with troublesome dyskinesia compared to IR CD-LD in any subgroup (P>.14). **CONCLUSIONS:** Advanced PD patients reported higher global impression of change and greater improvements in "off" time without worsening troublesome dyskinesia after treatment with IPX066 compared with IR CD-LD, regardless of disease severity subgroup.

PND9

THE EFFICACY OF MELATONIN FOR PRIMARY INSOMNIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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OBJECTIVES: We performed a systematic review of randomized controlled trials (RCTs) to estimate the efficacy of melatonin versus placebo or other hypnotic agents on the improvement of sleep quality and quantity in patients with primary insomnia. **METHODS:** We searched the published literatures in eight electronic databases, including Ovid-Medline, EMBASE, the Cochrane Library, and five Korean databases through October 2014. We included articles comparing efficacy for sleep between melatonin and placebo or other hypnotics among primary insomnia patients. The quality of studies was evaluated by using the Cochrane's risk of bias. The mean difference (MD) or standardized mean difference (SMD) was calculated using the random-effects method for each study outcome. To assess heterogeneity of inter-trial, we used the I2-statistic. Subgroup-analyses were performed by assessment tools, study designs, ages and dosage of melatonin. Funnel plots were used to assess publication bias. **RESULTS:** Eighteen RCTs were identified and the comparison groups of all included trials were placebo. Compared with placebo, melatonin significantly reduced sleep onset latency (MD: -6.58 min [95% confidential interval (CI): -9.75 to -3.41], p < 0.0001), and increased total sleep time (MD: 20.56 min [95% CI: 4.70 to 36.41], p = 0.01) and sleep efficiency (MD: 3.47% [95% CI: 0.37 to 6.58], p = 0.03). Sleep quality was also improved (SMD: 0.22 [95% CI: 0.03 to 0.40], p = 0.02) in melatonin group but this result was concluded based on a small number of studies. In subgroup-analyses for each outcome, there was no clinically remarkable finding. We did not find any evidence of statistical heterogeneity and publication bias. **CONCLUSIONS:** Melatonin showed to be effective for sleep in comparison with placebo, thus can be an effective option for the treatment of insomnia. Further studies are needed to conclude safety profiles, economic usefulness and tolerance of melatonin.

PND10

COMPARISON OF CLINICAL EFFECTIVENESS OF TREATMENTS FOR PSEUDOBULBAR AFFECT (PBA) Â€“ RESULTS FROM A SYSTEMATIC REVIEW

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OBJECTIVES: PBA is a neurologic disorder characterized by involuntary, uncontrollable laughing and/or crying episodes that are often incongruent with the patient's internal emotional state; PBA has also been called pathological laughing/crying, emotionalism, etc. Until FDA approval of dextromethorphan/quinidine (DM/Q) in 2010, multiple agents including antidepressants, antipsychotics, dopamine agonists and sedatives were used off-label for the management of PBA symptoms. We conducted a systematic review of therapies (licensed and unlicensed) for PBA symptoms to evaluate their relative clinical effectiveness **METHODS:** Databases: Medline, Medline in process, Embase and the Cochrane central register of controlled trials; conference abstracts were searched in Embase. Study type: RCTs and non-RCTs in adult patients with PBA/PBA-like symptoms (pathological laughing/crying, emotionalism, etc). Interventions: DM/Q, antidepressants, antipsychotics, dextromethorphan and quinidine alone. Outcome measures: change from baseline in various measures of PBA/emotionalism symptoms or symptom burden (NPI, SF-36, PRS scores and the caregiver strain index (CSI)). **RESULTS:** Nine RCTs and three observational studies were included. Among off-label drugs, six RCTs of 3 SSRIs and 2 TCAs showed improvements in disparate PBA symptom measures, only 1 used a validated symptom measure. These studies were small (N=6-28) using mostly stroke patients. They were heterogeneous on how they defined/diagnosed PBA and varied in duration (1.4-24 weeks). As such, no formal evidence synthesis was possible. Three RCTs and one open label trial investigating DM/Q included a well-defined and diverse PBA patient population, showing statistically significant improvements in a range of validated clinical and HRQoL outcomes relevant for the treatment of PBA. **CONCLUSIONS:** The evidence base for off-label agents used for treatment of PBA is limited, relying on small often uncontrolled studies showing ill-defined treatment effects and little or no safety tracking. DM/Q is the only treatment for PBA that has demonstrated efficacy in well-conducted clinical trials in patients with varied neurological disorders.

PND11

TERIFLUNOMIDE SHOWS CONSISTENT CLINICAL EFFICACY ON SEVERE RELAPSES ACROSS TEMSO AND TOWER: 2 PHASE 3 TRIALS

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OBJECTIVES: Teriflunomide is a once-daily oral immunomodulator approved for relapsing-remitting MS. Here we report the key efficacy, safety, and post hoc analyses from the randomized, placebo-controlled phase 3 trials TEMSO (NCT00134563) and TOWER (NCT00751881). **METHODS:** In TEMSO/TOWER, a total of 1088/1169 patients with relapsing MS were randomized (1:1:1) to once-daily teriflunomide 14 mg, teriflunomide 7 mg, or placebo. Treatment duration was 108 weeks (TEMSO) or variable, based on time of enrollment (TOWER; 48–152 weeks, ending 48 weeks after last patient randomized). Primary and key secondary endpoints were annualized relapse rate (ARR) and disability progression confirmed for 12 weeks. Additional endpoints included safety and tolerability. Post hoc analyses examined the effect of teriflunomide on 5 severe relapse outcomes: (A) relapses with sequelae defined by increase in Expanded Disability Status Scale score/Functional Score 30 days postrelapse; (B) relapses with investigator-defined sequelae; (C) severe relapses by Panitch definition; (D) relapses leading to hospitalization; and (E) relapses requiring treatment with intravenous corticosteroids. **RESULTS:** In TEMSO/TOWER, teriflunomide 14 mg significantly reduced both ARR and disability progression vs placebo. Teriflunomide 7 mg significantly reduced ARR but not disability progression. Teriflunomide 14 mg significantly reduced annualized rates of severe relapse outcomes compared with placebo in TEMSO/TOWER by: (A) 36.2% (P=0.0011)/36.6% (P=0.0021); (B) 52.6% (P<0.0001)/53.5% (P=0.0004); (C) 38.5% (P=0.0286)/52.5% (P=0.0015); (D) 59.3% (P<0.0001)/33.6% (P=0.0155); and (E) 33.7% (P=0.0003)/35.7% (P=0.0002). Teriflunomide 7 mg also reduced annualized rates of severe relapses, although not significantly in all definitions. Both teriflunomide doses showed similar safety profiles across the 2 studies. **CONCLUSIONS:** Teriflunomide 14 mg has shown consistent and significant positive effects on ARR and disability progression in 2 phase 3 studies. Teriflunomide also reduces severe relapses as measured by various relapse definitions, which may reduce relapse-related healthcare costs and improve patients' quality of life.

PND12

ESTIMATION OF TIME TO REACH RRMS EDSS HEALTH STATES ≥ 7.0 OR SPMS FOR DELAYED-RELEASE DIMETHYL FUMARATE

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OBJECTIVES: Multiple sclerosis (MS) disease progression is measured by the Expanded Disability Status Scale (EDSS). UK MS clinical guidelines1recommend that patients discontinue treatment with disease modifying therapies (DMTs) on reaching EDSS ≥7.0, or experiencing non-relapsing secondary progressive MS (SPMS). This study derived the time for patients to reach EDSS ≥7.0 or SPMS from EDSS 4.0 or 5.0, for patients treated with delayed-release dimethyl fumarate 240mg (DMF; also known as gastro-resistant DMF), or no DMT treatment. **METHODS:** The time taken to reach relapsing-remitting MS (RRMS) EDSS ≥7.0, or SPMS (any EDSS state) from EDSS 4.0 or 5.0 was estimated from transition probability matrices using algebraic techniques from Mandel 20072: the time to EDSS ≥7.0 or SPMS was derived for each matrix (DMF, untreated) by using matrix multiplication to estimate the proportion of patients who had reached these states over time. The transition matrix for untreated patients was derived using placebo arm data from clinical trials3,4(for RRMS population) and London Ontario dataset (for transitions from RRMS to SPMS). The transition matrix for DMF was estimated by applying treatment effect on disability progression (sourced from a mixed treatment comparison), to the probability of progressing in the untreated matrix. Probabilistic sensitivity analysis was conducted to estimate 95% confidence intervals (CIs). **RESULTS:** The time for progression from EDSS 4.0 to ≥7.0 or SPMS was 8.53 years (95% CI: 7.05-10.25) for patients treated with DMF and 5.90 years (95% CI: 5.59-6.24) for untreated patients. The time from EDSS 5.0 to ≥7.0 or SPMS was 5.28 years (95% CI: 4.32-6.37) for patients treated with DMF and 3.64 years (95% CI: 3.34-3.96) for untreated patients. **CONCLUSIONS:** Our analysis showed that DMF therapy was associated with a longer time interval between EDSS 4.0 or 5.0 and progression to EDSS ≥7.0 or SPMS relative to no DMT treatment.

PND13

"NUMBER NEEDED TO TREAT" ANALYSIS TO ASSESS THE COMPARATIVE OUTCOMES FROM TERIFLUNOMIDE AND DIMETHYL FUMARATE STUDIES IN RELAPSING MULTIPLE SCLEROSIS

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OBJECTIVES: Teriflunomide and dimethyl fumarate (DMF), oral therapies for relapsing-remitting MS, have demonstrated efficacy in clinical trials on magnetic