SciMedCentral

Annals of Neurodegenerative Disorders

Research Article

Concomitant Medication Use in Progressive Supranuclear Palsy Clinical Trial Participants

Michael Gold[1], Catherine Gauthier-Campbell, and Bruce H. Morimoto[2]*

[1]*Global Product Development, PPD, Inc., USA*
[2]*Drug Development Services, Celerion, Inc., USA*

***Corresponding author**
Bruce H. Morimoto, Drug Development Services, Celerion, Inc., USA, Tel: 650-298-8430; Email: bhmorimoto@gmail.com

Submitted: 21 October 2016
Accepted: 07 November 2016
Published: 09 November 2016

Keywords
- Polypharmacy
- Concomitant medication
- Treatments
- Adverse reactions
- Drug-drug interactions

Abstract

Progressive Supranuclear Palsy (PSP) is a rare and progressive movement disorder pathologically characterized by tau tangles for which there are no effective therapies. Emerging therapies for Alzheimer's Disease are increasingly focus on tau and consequently, PSP has emerged as an attractive patient population in which to test novel tau-directed therapies.

There are currently no approved therapies for PSP; however, most PSP patients are treated with multiple medications to address some of the symptoms of PSP and comorbidities found in this patient population. The risks of polypharmacy to patient safety as well as clinical trial outcome measures are clearly evident. Data on medication use extracted from an interventional study in subjects with PSP revealed that PSP patients were on an average (SD) of 8.5 (4.7) medications at the time of enrollment in to the study. Dopaminergic agents and antidepressants were the two most common classes of medications used by 53% and 46% of subjects respectively. Approximately a third of subjects enrolling in this study were on a potentially inappropriate medication. A substantial number of subjects were on combinations of medications known to be associated with adverse reactions due to drug-drug interactions. Given their particular susceptibility to the consequences of polypharmacy, clinicians and pharmacists need to be aware and cautious about the treatment of PSP patients. Additionally, it is important to recognize these concomitant medications when formulating the inclusion-exclusion criteria for clinical trials.

ABBREVIATIONS

PSP: Progressive Supranuclear Palsy; DA: Dopaminergic; PD: Parkinson Disease; ATCC: Anatomical Therapeutic Chemical Classification; SD: Standard Deviation; NSAID: Non-Steroidal Anti-Inflammatory Drug; PIM: *Potentially Inappropriate Medication; OTC: Over-the-Counter; CNS: Central Nervous System*

INTRODUCTION

Progressive Supranuclear Palsy (PSP) is a relatively rare, rapidly progressive neurodegenerative disorder characterized by axial rigidity, loss of balance, autonomic dysfunction, eye movement abnormalities and cognitive impairment [1]. Due to its phenotypic similarity to Parkinson Disease (PD), most patients with PSP are initially misdiagnosed with PD and treated with dopaminergic compounds (DA) [2]. Clinical observations suggest that PSP patients either fail to respond to DAs or have a very limited, transient response to them. PSP patients develop a myriad of additional symptoms associated with disease progression [3] and in the absence of disease-modifying treatments, clinicians attempt to manage patients on a symptomatic basis [4]. In addition, PSP patients are also susceptible to other age-related disorders resulting in the potential for wide-spread polypharmacy.

Polypharmacy in the elderly is a highly prevalent, well known and recognized problem [5] associated with increased risks for adverse events including falls [6], cognitive impairment, delirium [7] and death [8]. Given the fact that PSP patients are already predisposed to such poor outcomes, the impact of polypharmacy on PSP patients appears to be under-recognized and is in need of more aggressive attention and management.

Although there are data, either anecdotal or from small pilot studies, regarding the potential efficacy of a large number of compounds, none of these data provide compelling evidence of efficacy. Despite the lack of efficacy of these compounds, it appears certain compounds are commonly used in PSP patients. A somewhat dated, single-center, retrospective review from a center with expertise in PSP [9] reported data on 136 patients of whom 87(64%) provided adequate drug-response data. In these 87 patients, amitriptyline, imipramine and levodopa/carbidopa were the three most common medications used with a benefit reported in 32%, 28% and 32% of patients respectively. A review of putatively effective medications in patients with

autopsy-proven PSP by Kompoliti and colleagues [10] revealed that out of 12 patients, 11 patients received L-DOPA with only 1 patient having a marked (albeit short-lived) response, 3 had a moderate response and 6 experienced either an exacerbation of their PSP or related symptoms. Six of the 12 patients received bromocriptine resulting in a modest benefit in one patient and marked deterioration in another. Five of the 12 patients received amantadine resulting in a questionable improvement in 2 patients and deterioration in three patients. The authors conclude that given the lack of efficacy seen with single neurotransmitter replacement strategies, that combination therapies may represent a potential avenue to improve treatments. A more recent review [11] of the literature of symptomatic treatments for PSP clearly illustrates the problem with symptomatic efficacy data, both in terms of the lack of high quality, paucity of prospectively powered clinical trials and the relatively small numbers of patients in the studies that have been reported, reinforcing the conclusion that current symptomatic therapies for PSP are generally ineffective.

Despite mixed efficacy outcomes, PSP patients are routinely prescribed a plethora of medication, and the benefits of this common polypharmacy practice may not outweigh the risks. Excessive polypharmacy may lead to inappropriate use of medication, increased side effects and drug-drug interactions, especially in older populations with multiple comorbidities.

Although there is some evidence for the correlation between polypharmacy and negative clinical outcomes in the elderly [12], there are no recent or systematic reviews of medications being used by PSP patients in terms of the number, class or duration of use. Such data may be useful to clinicians managing PSP patients as a way to sensitize them to the variety of medications that their patients are likely to be taking and their possible interactions. In addition, these data should be useful to sponsors planning clinical trials in PSP in order to develop more appropriate inclusion/exclusion criteria, plan for adequate safety monitoring and account for the potential of medication use to affect the accuracy and precision of clinical outcome measures.

MATERIALS AND METHODS

Data on concomitant medications were extracted from the clinical trial database for study AL-108-231. Study AL-108-231 is a placebo-controlled, parallel-group, 12-month study of davunetide (AL-108) in patients with probable or possible PSP sponsored by Allon Therapeutics Inc. Details of the study were published [13]. Subjects enrolling in this study were not allowed to be on certain classes of medications as follows: subjects could not start treatment with memantine, acetylcholinesterase inhibitors, antipsychotic agents (other than quetiapine), mood stabilizers or benzodiazepines within 4 weeks of screening or during the study. Treatment with lithium, methylene blue, tramiprosate, ketone bodies, or putative disease-modifying agents directed at tau within 90 days of screening or during the course of the study was prohibited. Cancer chemotherapy and systemic corticosteroids for longer than one week were prohibited. Chronic narcotic treatment was also prohibited, but use up to 14 days for acute pain was allowed when prescribed by a health care provider.

The following information was used in the subsequent analyses: Subject ID, trade name, generic name, ATCC code, verbatim indication, start date and duration of use up to randomization. Dose, dosage units and frequency of dosing were collected, but not used for analysis.

Trade names that were not immediately recognizable were searched for in order to identify the appropriate generic name or components. Searches for generic names relied heavily on the following two sites: www.nlm.nih.gov and www.drugs.com. All medications used were coded using the Anatomical Therapeutic Chemical Classification System by a contract research vendor using their standard operating procedures. The ATCC system allows a single compound to have multiple classifications based on its pharmacology and chemical structure. It is possible that the same compound could be used for multiple indications (ie. acetylsalicylic acid could be used for its anti-inflammatory or its anti-platelet activity). Therefore, ATCC codes that reflect a compound's chemical class were reviewed in the context of the clinical condition (indication) for which the compound was being used and the most relevant pharmacological ATCC code was applied. For example, when aspirin was used and the indication was heart attack prevention, the ATCC code "PLATELET AGGREGATION, EXCLUDING HEPARIN" was used and when aspirin was used to manage pain, the ATCC code "ANALGESICS AND ANTIPYRETICS" was used. Although it might be possible to predict some drug-drug interaction on the basis of chemical structure, it is our premise that most clinicians are not facile with chemical structure, but are much more likely to recognize the potential for drug-drug interactions based on pharmacological classes and their known side-effect profiles.

A similar review was performed on the indications for medication use in order to eliminate redundant or synonymous verbatim terms and provide a more parsimonious view of the various clinical conditions that afflict PSP patients (i.e. UTI and Urinary Tract Infection, Heartburn and Gastro-esophageal Reflux).

Only data from medications being used prior to entry into the clinical trial were used for this analysis in order to a) prevent any potential unblinding bias, b) present a cross-sectional view of medication use and c) prevent confounding new medication use with disease progression.

RESULTS AND DISCUSSION

A total of 3833 separate medication records were identified of which 2630 had a start date or duration of use indicating that the medication was being used prior to entry into the AL-108-231 study.

These 2630 medication records represent data from 312 subjects in the AL-108-231 study. Descriptive demographic data on these 312 subjects are presented in Table (1). Subjects included in this analysis were on an average (SD) of 8.5(4.7) medications with a median and range of 8 and 30 medications at the time of entry into the AL-108-231 study.

These 2630 medication records represented 300 clinical "indications" of which the 20 most common (1928/2630, ~73%) are summarized in Table (2). The data also encompassed 139 ATCC classes of which the 30 most common (1889/2630, ~72%)

Table 1: Subject Demographics (from AL-108-231, ref 13).

Age (years)		**Baseline PSPRS**	
n	312	n	312
Mean (SD)	68 (6.6)	Mean (SD)	40 (10.8)
Median (Min, Max)	68 (45, 84)	Median (Min, Max)	39 (12, 73)
Age Category - n (%)		< 40 - n (%)	167 (53.5)
<65	98 (31.4)	Baseline SEADL	
>=65	214 (68.6)	n	312
Sex - n (%)		Mean (SD)	0.5 (0.22)
Male	165 (52.9)	Median (Min, Max)	0.5 (0.1, 1.0)
Female	147 (47.1)	Region - n (%)	
Ethnicity - n (%)		Australia	14 (4.5)
Hispanic or Latino	3 (1.0)	Europe	95 (30.4)
Non-Hispanic or Non-Latino	285 (91.3)	North America	203 (65.1)
Not Reported	24 (7.7)	Modified Hachinski Score - n (%)	
Race - n (%)		0	115 (36.9)
Asian	8 (2.6)	1	155 (49.7)
Black	5 (1.6)	2	34 (10.9)
Not Reported	21 (6.7)	3	8 (2.6)
Other	4 (1.3)	MMSE	
White	274 (87.8)	n	312
Height (cm)		Mean (SD)	26 (3.5)
n	312	Median (Min, Max)	27 (15, 30)
Mean (SD)	169.1 (9.68)	CoQ10 use - n (%)	
Median (Min, Max)	168.0 (143.5, 199.4)	Use	62 (19.9)
Weight (kg)		No Use	250 (80.1)
n	312	Tau Haplotype n (%)	
Mean (SD)	77.6 (16.38)	H1/H1	230 (73.7)
Median (Min, Max)	77.6 (44.8, 140.0)	H1/H2	14 (4.5)
		H2/H2	0
		Missing	68 (21.8)

Abbreviations: PSPRS: Progressive Supranuclear Palsy Rating Scale; CoQ10: Coenzyme Q10; Min: minimum; Max: maximum; SD: standard deviation

Table 2: Indications by frequency.

Indication	**Count**	**%**
SUPPLEMENT	435	16.5
PROGRESSIVE SUPRANUCLEAR PALSY	319	12.1
HYPERTENSION	271	10.3
DEPRESSION	112	4.3
HYPERCHOLESTEROLEMIA	92	3.5
GENERAL HEALTH	73	2.8
INSOMNIA	65	2.5
CONSTIPATION	63	2.4
DIABETES	61	2.3
CARDIAC PROPHYLAXIS	60	2.3
HYPOTHYROIDISM	47	1.8
OSTEOPOROSIS	46	1.8
GASTROESOPHAGEAL REFLUX	44	1.7
BENIGN PROSTATIC HYPERPLASIA	43	1.6
PAIN	40	1.5
ARTHRITIS	40	1.5
DRY EYES	38	1.4
PARKINSONISM	36	1.4
HYPERLIPIDEMIA	24	0.9
SEASONAL ALLERGIES	19	0.7

are summarized in Table (3). Of the 319 records that have an indication of PSP, the 10 most common ATCC codes linked to the indication of PSP are listed on Table (4).

The proportion of subjects in this study using Potentially Inappropriate Medications (PIM) based on the updated Beers criteria [14] was calculated by matching the generic name of drugs being used by a subject with the generic names included in the Beers criteria. Of the 310 subjects included in this analysis, 92 were on at least one PIM. The most common PIMs (~70%) were NSAIDS (n=21, 23%), antidepressants (n=19, 21%), anxiolytics (n=16, 17%) and urinary antispasmodics (n=8, 9%).

Data from the AL-108-231 clinical trial in PSP indicate that there is pervasive polypharmacy in these patients. Since these data are derived from subjects who were able to enroll in a clinical trial and in whom certain classes of medications were not allowed, it is likely that the degree of polypharmacy is under-estimated. The degree of polypharmacy may also be under-estimated because the study restricted the severity of PSP in patients who enrolled and it is likely that more medications will be tried/used as the patient progresses and experiences additional morbidity. Within the context of the data presented here, it is apparent that most PSP patients are treated and maintained on dopaminergic agents whether they be directly acting (i.e. L-DOPA,

Table 3: ATCC Code by frequency with mean (SD) duration of use.

ATCC Code	Count (%)	Mean (SD) Duration (days)	Number of subjects(%)
DOPA AND DOPA DERIVATIVES	194 (7.4)	585.77 (571)	164 (53)
ANTIDEPRESSANTS	172 (6.54)	673.16 (848)	142 (46)
PLATELET AGGREGATION INHIBITORS EXCL. HEPARIN	120 (4.56)	2443.75 (2578)	117 (38)
OTHER THERAPEUTIC PRODUCTS	111 (4.22)	1193.43 (1403)	65 (21)
HMG COA REDUCTASE INHIBITORS	105 (3.99)	1954.61 (2071)	109 (35)
VITAMIN D AND ANALOGUES	88 (3.35)	1145.52 (1399)	88 (28)
ANTIINFLAMMATORY AGENTS, NON-STEROIDS	77 (2.93)	1756.58 (2353)	69 (22)
OTHER LIPID MODIFYING AGENTS	66 (2.51)	1613.14 (1686)	64 (21)
VARIOUS ALIMENTARY TRACT AND METABOLISM PRODUCTS	64 (2.43)	704.09 (931)	62 (20)
ACE INHIBITORS, PLAIN	62 (2.36)	1629.66 (1672)	74 (24)
DOPAMINERGIC AGENTS	57 (2.17)	547.44 (384)	76 (250
MULTIVITAMINS, PLAIN	55 (2.09)	3015.40 (3005)	48 (15)
THYROID HORMONES	51 (1.94)	2772.88 (2982)	48 (15)
PROTON PUMP INHIBITORS	50 (1.9)	1342.62 (1451)	48 (15)
BETA BLOCKING AGENTS, SYSTEMIC	50 (1.9)	2414.40 (2564)	49 (16)
ANALGESICS AND ANTIPYRETICS	50 (1.9)	1367.62 (2417)	46 (15)
BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS	49 (1.86)	1448.90 (1308)	32 (10)
OTHER OPHTHALMOLOGICALS	43 (1.63)	676.79 (1215)	31 (10)
DIURETICS	41 (1.56)	1190.46 (1383)	40 (13)
ANTIBACTERIALS FOR SYSTEMIC USE	41 (1.56)	154.76 (482)	30(10)
CYANOCOBALAMIN AND ANALOGUES	40 (1.52)	971.40 (1096)	40 (13)
CALCIUM	37 (1.41)	2523.78 (1950)	63 (20)
SELECTIVE CALCIUM CHANNEL BLOCKERS WITH MAINLY VASCULAR EFFECTS	36 (1.37)	1753.81 (2049)	47 (15)
LAXATIVES	36 (1.37)	906.56 (1315)	32 (10)
URINARY ANTISPASMODICS	35 (1.33)	650.77 (773)	34 (11)
HYPNOTICS	34 (1.29)	901.26 (935)	32 (10)
ALPHA-ADRENORECEPTOR ANTAGONISTS	34 (1.29)	992.97 (990)	34 (11)
DOPAMINE AGONISTS	32 (1.22)	804.09 (902)	29 (9)
DRUGS AFFECTING BONE STRUCTURE AND MINERALIZATION	30 (1.14)	1526.60 (1503)	30 (10)
ANGIOTENSIN II ANTAGONISTS, PLAIN	29 (1.10)	1718.97 (1523)	29 (9)

Table 4: ATCC Code by frequency with mean (SD) duration of use for PSP as an indication.

ATCC Code	Count	Mean Duration	SD Duration
DOPA AND DOPA DERIVATIVES	166	565.83	557.16
DOPAMINERGIC AGENTS	48	550.58	391.34
VARIOUS ALIMENTARY TRACT AND METABOLISM PRODUCTS	25	563.36	624.82
DOPAMINE AGONISTS	20	824.75	1081.77
MONOAMINE OXIDASE B INHIBITORS	18	483.61	256.52
ANTIDEPRESSANTS	9	590.78	537.18
ANXIOLYTICS	6	292.17	409.68
CENTRALLY ACTING SYMPATHOMIMETICS	4	176.75	170.78
ANTICHOLINESTERASES	4	786.75	318.81
MUSCLE RELAXANTS	3	518.33	738.49
OTHER OPHTHALMOLOGICALS	2	1033.00	0.00

ropinirole) or indirectly acting (i.e. amantadine). The data also indicate that antidepressants of nearly every pharmacological class (SSRI, SNRI, NSSRI) are used in PSP patients for a variety of "indications" including depression, anxiety, insomnia, agitation and apathy almost as often as dopaminergic agents. The ATCC category "VARIOUS ALIMENTARY TRACT AND METABOLISM PRODUCTS" coded nearly exclusively to Coenzyme Q10 use and indicates fairly wide-spread use despite the modest treatment effect observed in a short-term treatment study [15].

PSP patients appear to be susceptible to common age-related disorders as noted by the relatively frequent indications of hypertension, hypercholesterolemia, diabetes and arthritis. The treatment of these medical co-morbidities is reflected in the common use of various classes of antihypertensives, lipid/cholesterol lowering agents, oral hypoglycemics and non-steroidal anti-inflammatory drugs. The very high use of platelet-aggregation inhibitors is driven by extensive use of aspirin for "cardio protection". PSP patients are also eager consumers of nutritional supplements of every type. Unfortunately, it is not possible to identify the active ingredients in many of these supplements.

With this degree of polypharmacy, drug-drug interactions are very likely and could potentially lead to adverse events in patients who by nature of their underlying PSP are not likely to cope well (see Table 5). Based on reviews of efficacy, the benefits of keeping patients on dopaminergic medications may not outweigh the side effects. DA agents are commonly associated with nausea and vomiting [16] which is particularly problematic in PSP patients who cannot properly protect their airways and who have underlying autonomic problems. In addition, DA agents have also been reported to cause dystonia and to exacerbate eye-lid opening in PSP patients [17]. The same issues apply to the use of antidepressants given the lack of compelling evidence that these medications work in patients with PSP yet have well known side effects. There are also potential problems when medications are used to control particular symptoms such as bladder urgency or excess salivation since these compounds have known side effects on muscle tone, blood pressure and cognition.

In rare cases, drug-drug interactions can cause potentially serious or even fatal adverse reactions. The concomitant use of serotonergic agents, such as serotonin reuptake inhibitor, monoamine oxidase inhibitors and tricyclic antidepressants may increase the risk of serotonin syndrome [18]. Symptoms of the serotonin syndrome may include altered consciousness, hallucination, coma, tachycardia, hyperthermia, myoclonus, tremor, rigidity, abdominal cramping, vomiting, diarrhea and death. Approximately 7% of patients in the AL-108-231 study were taking at least two drugs at baseline that could cause hyper-stimulation of brainstem 5-HT1A and 2A receptors and lead to a serotonin syndrome.

The co-administration of compounds that competitively bind to the same target or are metabolized by the same enzyme may cause interference or potentiation of the activity of each compound. For example, the concomitant use of amlodipine and simvastatin, which are both metabolized by CYP450 3A4, may significantly increase the plasma concentrations of simvastatin and increase the risk of statin-induced myopathy [19]. Similarly, the administration of SSRI antidepressants (fluvoxamine for example) inhibits the metabolism of the anticoagulant agent warfarin through the CYP450 2C9 isoenzyme, leading to increased risks of bleeding [20]. Co-administration of agents that can cause prolongation of the QT interval may result in increased risk of ventricular arrhythmias, including torsades de pointes and sudden death [21]. Conversely, the use of low-dose aspirin for cardioprotective effects may be antagonized by co-administration of some non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen [22].

NSAIDs, corticosteroids and diuretics are also known to reduce the efficacy of most classes of antihypertensive medications [23]. This is particularly relevant in an aging PSP population, where hypertension is one of the most common conditions.

The concomitant use of central nervous system (CNS) depressants, such as anxiolytics, antipsychotics, antihistamines and antitussives (centrally-acting codeine), may result in additive toxicity, enhanced sedation, impaired psychomotor skills and respiratory depression[23].Similarly, additive toxicity has been seen in patients taking a combination of antidepressants (SSRIs) and NSAIDs, with enhanced risks for gastro-intestinal mucosal erosion and bleeding [24]. Given the number of PSP patients taking some class of antidepressant (46%), the risk of additive adverse reactions may not outweigh the potential benefits.

The wide-spread use of vitamins, nutritional supplements and herbal medicines represents an additional challenge to clinicians who manage PSP patients as it is not uncommon for patients not to disclose non-prescription medications [25]. Data collected by the Slone survey indicate that about 47% of men over 65 years of age and 59% of women over age 65 use some form of vitamins or mineral supplements [26]. A rough estimate of similar usage in these PSP subjects is about 76% suggesting that PSP patients are likely to exceed average use of OTC medications. Supplements, herbal medications and OTC medications may contain pharmacologically active agents or contaminants [27], some of which may also be CNS-active [28], so it is important

Table 5: Most common drug-drug interactions that associated with major risk.

Med 1	Med 2	Possible Risk	Count	%
Co-administration of agents with serotonergic activity (i.e. SSRI, SNRI, TCA, MAO-B inhibitors)		Serotonin syndrome	21	7%
IBUPROFEN	ACETYLSALICYLIC ACID	Serious gastrointestinal toxicity, loss of cardioprotective effects	14	4%
AMLODIPINE	SIMVASTATIN	Musculoskeletal toxicity, myopathy and rhabdomyolysis	7	2%
QUETIAPINE	CITALOPRAM	QT interval prolongation, ventricular arrhythmias including torsades de pointes	5	2%
AZITHROMYCIN	CITALOPRAM			
CIPROFLOXACIN	CITALOPRAM			

Abbreviations: SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: Serotonin Norepinephrine Reuptake Inhibitor; TCA: Tricyclic Antidepressant; MAO-B: Monoamine Oxidase B

that clinicians inquire about non-prescription medications on a regular basis.

It appears that the calls for trials of single agents or trials [29] of combination therapy [11] have made the leap from suggestions into de-facto clinical practice with little, if any, robust clinical trial data to support that practice. Current clinical practices identified via this analysis may impact the ability of PSP patients to participate in future clinical trials. Some of the medications commonly used in PSP patients may have potential disease-modifying effects (i.e. MAO-B inhibitors, anti-oxidants), some may have effects on symptoms (i.e. muscle relaxants, hypnotics) that may not be constant or sustained, thereby introducing added variability into clinical trials.

Lastly, from a safety perspective the substantial amount of polypharmacy reported here indicates that much more attention needs to be paid by clinicians and pharmacists to potential drug-drug interactions based on drug-induced induction or inhibition of clearance mechanisms, age-related changes in drug clearance or metabolism [30] and pharmacodynamic interactions in order to prevent iatrogenic adverse drug reactions [31]. The fact that nearly 1/3 of subjects enrolling in this study were on at least one PIM is concerning. The Beers criteria are agnostic as to diagnosis; therefore, one could argue that in the context of the morbidity associated with PSP, some use of PIMs may be appropriate. This argument would carry weight only if there were robust data that PSP patients benefitted from use of PIMs. Since PSP patients tend to be managed by teams of physicians, a program of de-prescribing [32] or some of the techniques described by Topinkova and colleagues [33] might be an option to try to reduce the degree of polypharmacy in these patients.

There are limitations to this analysis that readers should keep in mind. As noted, these data are derived from subjects with PSP who enrolled in an interventional clinical trial. Although there are data suggesting that subjects who agree to enroll in clinical trials in dementia [34] may differ from those who don't, the baseline demographic data from subjects included in this report match those of other PSP clinical trial cohorts [35] as well as longitudinal cohorts [35] indicating that these are typical PSP patients. Given the restrictions in the kinds of medications that were allowed in this study and the severity of PSP, there are likely to be systematic differences between the medications used by these subjects and those used in an unselected PSP population.

Approximately ~2/3 of subjects were recruited from the United States and Canada and the rest from Western Europe and a single site in Australia; therefore, the data may over-represent North American clinical practice. Since the study was conducted in academic centers with movement disorder expertise, the data are likely to also reflect a more academic/specialty type of clinical practice rather than a community-based practice.

CONCLUSION

Polypharmacy is prevalent in the aging population and the PSP patients are no exception. In a Phase 2/3 clinical trial of 312 PSP patients (study AL-108-231), the PSP trial participant was taking an average 8.5 medications, which is similar to the general geriatric population. Medications were prescribed for numerous indications and surprisingly, PSP was the second most frequent indication at 12.1% even though, there are no approved drugs for PSP. This suggests that attempts are made to control the various symptoms of the disease. The proportion *of subjects in this study using Potentially Inappropriate Medications was approximately ~30%.* Unfortunately, drug-drug interactions can exacerbate side effects or toxicity, and potentially diminish the therapeutic efficacy of certain drugs. Given the number of concomitant medications prescribed to PSP patients, additional scrutiny on the part of clinicians and pharmacists is warranted.

ACKNOWLEDGEMENTS

The authors thank all the participants, their families, caregivers and investigators for their support of the AL-108-231 PSP study. The AL-108-231 study was funded by Allon Therapeutics Inc.

Conflict of Interest

Drs. Gold, Campbell and Morimoto were employees of Allon Therapeutics Inc.

REFERENCES

1. Rehman HU. Progressive supranuclear palsy. Postgrad Med J. 2000; 76: 333-336.
2. Barsottini OG, Felício AC, Aquino CC, Pedroso JL. Progressive supranuclear palsy: new concepts. Arq Neuropsiquiatr. 2010; 68: 938-946.
3. Martins IJ. Increased Risk for Obesity and Diabetes with Neurodegeneration in Developing Countries. J Mol Genet Med 2013.
4. Lubarsky M, Juncos JL. Progressive supranuclear palsy: a current review. Neurologist. 2008; 14: 79-88.
5. Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. Recent patterns of medication use in the ambulatory adult population of the United States: the Slone survey. JAMA. 2002; 287: 337-344.
6. Wang R, Chen L, Fan L, Gao D, Liang Z, He J, et al. Incidence and Effects of Polypharmacy on Clinical Outcome among Patients Aged 80+: A Five-Year Follow-Up Study. PLoS One. 2015; 10.
7. Lorenzl S, Füsgen I, Noachtar S. Acute confusional States in the elderly--diagnosis and treatment. Dtsch Arztebl Int. 2012; 109: 391-399.
8. Gnjidic D, Hilmer SN, Blyth FM, Naganathan V, Waite L, Seibel MJ, et al. Polypharmacy cutoff and outcomes: five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. J Clin Epidemiol. 2012; 65: 989-995.
9. Nieforth KA, Golbe L. Retrospective study of drug response in 87 patients with progressive supranuclear palsy. Clin Neuropharmacol. 1993; 16: 338-346.
10. Kompoliti K, Goetz CG, Litvan I, Jellinger K, Verny M. Pharmacological therapy in progressive supranuclear palsy. Arch Neurol. 1998; 55: 1099-1102.
11. van Balken I, Litvan I. Current and future treatments in progressive supranuclear palsy. Curr Treat Options Neurol. 2006; 8: 211-223.
12. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. Expert Opin Drug Saf. 2014; 13: 57-65.
13. Boxer AL, Lang AE, Grossman M, Knopman DS, Miller BL, Schneider LS et al. Davunetide in patients with progressive supranuclear palsy: a randomized, double-blind, placebo-controlled phase 2/3 trial. Lancet Neurol. 2014; 13: 676-685.
14. Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH.

Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. Arch Intern Med. 2003; 163: 2716-2724.

15. Stamelou M, Reuss A, Pilatus U, Magerkurth J, Niklowitz P, Eggert KM, et al. Short-term effects of coenzyme Q10 in progressive supranuclear palsy: a randomized, placebo-controlled trial. Mov Disord. 2008; 23: 942-9.

16. Miyasaki JM, Martin W, Suchowersky O, Weiner WJ, Lang AE. Practice parameter: Initiation of treatment for Parkinson's disease: An evidence-based review: Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2002; 58: 11-17.

17. Barclay CL, Lang AE. Dystonia in progressive supranuclear palsy. J Neurol Neurosurg Psychiatry. 1997; 62: 352-356.

18. Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med. 2005; 352: 1112-1120.

19. Gruer PJ, Vega JM, Mercuri MF, Dobrinska MR, Tobert JA. Concomitant use of cytochrome P450 3A4 inhibitors and simvastatin. Am J Cardiol. 1999; 84: 811-815.

20. Sansone RA, Sansone LA. Warfarin and Antidepressants: Happiness without Hemorrhaging. Psychiatry (Edgmont). 2009; 6: 24-29.

21. Yap YG, Camm AJ. Drug induced QT prolongation and torsades de pointes. Heart. 2003; 89: 1363-1372.

22. Catella-Lawson F, Reilly MP, Kapoor SC, Cucchiara AJ, DeMarco S, Tournier B, et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. N Engl J Med. 2001; 345: 1809-1817.

23. van Zwieten PA, Farsang C. Interactions between antihypertensive agents and other drugs. Blood Press. 2003; 12: 351-352.

24. Becker DE. Adverse drug interactions. Anesth Prog. 2011; 58: 31-41.

25. Schmiemann G, Bahr M, Gurjanov A, Hummers-Pradier E. Differences between patient medication records held by general practitioners and the drugs actually consumed by the patients. Int J Clin Pharmacol Ther. 2012; 50: 614-617.

26. Kantor ED, Rehm CD, Du M, White E, Giovannucci EL. Trends in Dietary Supplement Use Among US Adults From 1999-2012. JAMA. 2016; 316: 1464-1474.

27. Chan K. Some aspects of toxic contaminants in herbal medicines. Chemosphere. 2003; 52: 1361-1371.

28. Spinella M. The importance of pharmacological synergy in psychoactive herbal medicines. Altern Med Rev. 2002; 7: 130-137.

29. Golbe LI. Progressive Supranuclear Palsy. Curr Treat Options Neurol. 2001; 3: 473-477.

30. Turnheim K. When drug therapy gets old: pharmacokinetics and pharmacodynamics in the elderly. Exp Gerontol. 2003; 38: 843-853.

31. Ruiter R, Visser LE, Rodenburg EM, Trifiro G, Ziere G, Stricker BH. Adverse drug reaction-related hospitalizations in persons aged 55 years and over: a population-based study in The Netherlands. Drugs Aging. 2012; 29: 225-232.

32. Schuling J, Gebben H, Veehof LJ, Haaijer-Ruskamp FM. Deprescribing medication in very elderly patients with multimorbidity: the view of Dutch GPs. A qualitative study. BMC Fam Pract. 2012; 13.

33. Topinková E, Baeyens JP, Michel JP, Lang PO. Evidence-based strategies for the optimization of pharmacotherapy in older people. Drugs Aging. 2012; 29: 477-494.

34. Schoenmaker N, Van Gool WA. The age gap between patients in clinical studies and in the general population: a pitfall for dementia research. Lancet Neurol. 2004; 3: 627-630.

35. Bensimon G, Ludolph A, Agid Y, Vidailhet M, Payan C, Leigh PN; NNIPPS Study Group. Riluzole treatment, survival and diagnostic criteria in Parkinson plus disorders: the NNIPPS study. Brain. 2009; 132: 156-171.

36. Golbe LI, Ohman-Strickland PA. A clinical rating scale for progressive supranuclear palsy. Brain. 2007; 130: 1552-1565.

Cite this article

Gold M, Gauthier-Campbell C, Morimoto BH (2016) Concomitant Medication Use in Progressive Supranuclear Palsy Clinical Trial Participants. Ann Neurodegener Dis 1(4): 1017.