Manuscript Title

Adverse effects of anti-epileptics in trigeminal neuralgiform pain.

Authors

Tentolouris-Piperas V[1], Lee G[2], Reading J[2], O'Keeffe A G[3], Zakrzewska J M[4], Cregg R[5]

[1]Dementia Research Centre, Institute of Neurology, UCL, London, UK, [2]University College London Medical School, London, UK, [3]Department of Statistical Science, University College London, Gower St., London WC1E 6BT, [4]National Hospital for Neurology and Neurosurgery, Pain Management Centre, Eastman Dental Hospital, UCLH NHS Foundation Trust, London, UK

[5]Division of Brain Repair and Rehabilitation, Institute of Neurology, UCL, London, UK

Corresponding Author

Roman Cregg (r.cregg@ucl.ac.uk) Pain Management Centre, National Hospital for Neurology and Neurosurgery at Cleveland Street, 25 Cleveland Street, London W1T 4AJ.

Running title

Adverse effects of AEDs in pain

Abstract

Background: Side effects of anti-epileptic drugs (AEDs) have not been adequately documented in trigeminal neuralgia (TN) and its variants. The aim of this observational cross-sectional study was to compare the A-B Neuropsychological Assessment Schedule (ABNAS), which measures cognitive side effects to the Adverse Events Profile (AEP), which looks at a broader range of side effects, and to investigate drug/dosage relationships with questionnaire scores to help determine a point at which a drug change would be indicated. **Methods**: 105 patients were recruited from a facial pain clinic, over a ten-month period. Self-complete questionnaire scores were compared between patients using different AEDs. **Results**: ABNAS score correlated well with AEP indicating that cognitive side effects were a significant burden. Toxic range on the ABNAS was estimated to occur when scores were > 43/72 (95% CI: 37.4 to 48.6). Polytherapy is weakly associated with the higher scores. Oxcarbazepine dosage was found to linearly correlate with AEP and ABNAS scores, better than carbamazepine dosage. Memory alteration was least common with lamotrigine and oxcarbazepine, and there was less association between fatigue with oxcarbazepine/pregabalin. **Conclusion**: AEDs have significant side effects. The ABNAS questionnaire is a useful tool along with the AEP to recognize and monitor AEDs' side effects and to help to adjust medications to optimal dosage.

Main Body

Introduction

Trigeminal neuralgia (TN) is a condition characterized by recurrent unilateral episodes of electric shock-like pain, lasting from a few seconds to minutes in the distribution of the trigeminal nerve (1). The pain is often provoked by a slight and innocuous stimulus, such as touch. TN is usually idiopathic, but can present as a consequence of vascular abnormalities, tumours and multiple sclerosis.

There are other groups of conditions that are very similar to TN and in fact may be variants: short unilateral neuralgiform headache with conjunctival redness and tearing (SUNCT) and short unilateral neuralgiform headache with autonomic features (SUNA) (2).

First line drugs for idiopathic TN including SUNCT and SUNA are anti-epileptic drugs (AED), most commonly carbamazepine or oxcarbazepine (3). Alternative AEDs have been shown to be effective in TN, including lamotrigine (4), gabapentin (5), pregabalin (6) and baclofen (7). SUNCT and SUNA seem to respond particularly well to lamotrigine (2). Surgical treatment options for TN include microvascular decompression, stereotactic radiosurgery and percutaneous procedures such as glycerol rhizotomy, balloon compression, and radiofrequency thermocoagulation (8).

Medical treatment is perceived by patients as being a safer option and associated with fewer complications which are usually reversible, in contrast to surgery, which can have significant irreversible complications. This leads most patients and clinicians to lean towards a conservative treatment (9). However, this choice is made with scarce clinical evidence. One of the main reasons why patients opt for surgery is because of side effects from the AEDs (10) but little work has been done on this topic in TN. A qualitative survey conducted in 2001 (11) found that 100% of surveyed TN patients taking AEDs experienced side effects, including drowsiness and cognitive impairment, with a mean of three side effects per patient.

A systematic review on carbamazepine performed in 2011 (12) reported that 40 – 60 % of patients would exhibit adverse events, including those mentioned above, as well as gastrointestinal symptoms, headaches, dry mouth or taste change, and mood changes. Other reviews highlight the same problem (13-18). However, none of these include information on how the adverse events were measured or whether they were quantified or compared between drugs in any way. A recent systematic review looking at adverse events assessment on trials of gabapentin and pregabalin in post-operative pain highlighted that adverse event assessment method was not described in 18% of studies, and 8/90 studies did not report on adverse events at all (19).

In the epilepsy literature, side effects of AEDs are often measured using the Liverpool Adverse Events Profile (AEP) (Supporting material Figure 1) (20) which has been psychometrically tested. Ranging from 19 – 76, a score of 45 or higher is indicative of toxicity (21). It has only recently been used to investigate side effects of AEDs in TN (22).

However, the AEP does not enquire in depth on cognitive effects caused by the drugs, as its questions are mainly focused on other types of symptoms. The A-B Neuropsychological Assessment Schedule (ABNAS) (Supporting material Figure 2) includes questions on such symptoms (23, 24), but it has not been used in TN patients, nor has a cut-off score for toxic range been calculated yet.

In this study, we aim to use the AEP and ABNAS to quantitatively investigate adverse effects of AEDs used in TN and related conditions, and postulate a toxic range cut-off for the ABNAS.

Materials & Methods

Participants

Participants for this study were identified and consecutively recruited from a facial pain clinic in a London teaching hospital in the period between March and December 2015. Participants were asked to fill out an additional questionnaire, in addition to those that are routinely filled out during the follow up outpatient appointments. At this time point patients would have already been under treatment for at least three months, which is the interval between initial assessment and first follow-up.

In order to be included, patients had to have a diagnosis of trigeminal neuralgic pain (TN, SUNA, or SUNCT), be treated with AEDs, be above 18 years of age, have sufficient cognitive function and English language skills to accurately complete the surveys, have had an MRI scan excluding focal lesions or multiple sclerosis, and finally, to have verbally consented to participate in the research study. Patients were excluded if they suffered from a medical condition severe enough to prevent them from completing the study, had a history of drug or alcohol abuse, had signs or symptoms of a central neurological disorder, if they were unwilling to perform cognitive function tests, and finally, if they were prescribed medication other than AEDs that could affect cognitive functions, such as anti-depressants.

Although TN, SUNCT, and SUNA are considered to be different neurological conditions, there is evidence to support that they actually represent a variant of the same condition (25, 26), and ICD-11 acknowledges overlap between them. Furthermore, it is known that pain conditions often change after their onset (27) and that patients can often move between these phenotypes over time. At the time of referral to this specialist pain clinic, all patients would have had TN as the predominant diagnosis and would be under initial treatment based on the initial TN diagnosis. However, at the time of follow up the phenotype may have changed to SUNCT or SUNA. We elected to include all of these patients in this study, as our primary interest was to study the side effect profile of AED medications in these pain

conditions driven by trigeminal neuralgia. We have no reason to believe that AED side effects would differ significantly between these conditions.

Measures

The main measures of interest for this study were total scores of the AEP and ABNAS questionnaires. The order by which the two questionnaires were given to participants during their visit was alternated in a randomized manner. The ABNAS answers were assigned to categories of Slowing, Fatigue, Memory, Concentration, Motor and Language, as indicated by the questionnaire itself (23). Additionally, Brief Pain Inventory (BPI) – Facial (28, 29) and Hospital Anxiety and Depression Scale (HAD-A, HAD-D) (30) questionnaire scores were obtained as measures of pain relief, quality of life and mood. Mean score of the first four BPI questions was used as a primary measure for pain intensity as it is the standard measure used in most pain studies and the one used by the UK National Audit of Pain. Furthermore, these questions give a better estimate of pain severity in this case because TN is episodic. Pain scores were collected at the start of the outpatient review visit. Qualitative observations by participants and researchers alike were also obtained. The data was initially entered on an Excel spreadsheet on a secure server. The data was anonymized prior to analysis.

Statistical analysis

Statistical analysis was conducted using STATA 13 for Windows. Descriptive statistics were used to characterize the group's demographics, symptomatology, medications used, and questionnaire scores. As drug blood levels were not available for this study, indirect means were used to calculate a possible toxic range cut-off score for ABNAS. The toxic range cut-off point of the AEP was used to divide the study participants into two groups. The mean, median, standard deviation, and interquartile ranges of the ABNAS score in the toxic range group were used to approximate a similar cut-off score for ABNAS. For drug and dosage-specific analyses, a comparison of AEP, ABNAS, BPI, HAD-A, and HAD-D scores was

conducted between single- and multi-drug therapy subgroups using appropriate group-wise comparisons where necessary, either t-tests or Mann-Whitney U tests depending on the distribution of the measure of interest, in each group or subgroup compared. For the BPI analysis, different mean scores were calculated for each group of BPI questions: Mean pain intensity (Q1-Q4), mean general QOL Score (Q5a-Q5g), and mean facial score (Q5h-Q5n). Relationships between medication dosage and questionnaire scores were investigated using scatterplots and estimated correlation coefficients, although the study wasn't powered to assess the statistical significance, if any, of such relationships.

Results

Group demographics and questionnaire statistics

As a result of the above mentioned criteria, 105 patients were selected to be part of the study group. The demographics of this group and group statistics of the measures of interest are listed in Table 1. The majority of these patients had a diagnosis of trigeminal neuralgia (n=75), while the rest had other variants of neuropathic pain, such as SUNA (n=13), trigeminal neuralgia with concomitant pain (n=6), or in various combinations (n=11). In terms of medication, 78 patients were on monotherapy, while 27 were on polytherapy. The vast majority were treated with oxcarbazepine, carbamazepine, or lamotrigine, as shown in detail in Table 2 (Supporting material Figure 3).

	Total (N=105) Mean (SD)	**Female (N = 80) Mean (SD)**	**Male (N = 25) Mean (SD)**
Age	62.2 (11.5)	61.2 (11.5)	65.6 (11.2)
AEP total (19-76)	38.6 (10.7) (n=104)	38.9 (10.9) (n=79)	37.2 (10.4) (n=25)
ABNAS total (0-72)	27.8 (19) (n=98)	26.2 (18.5) (n=75)	33.3 (20) (n=23)
BPI mean pain intensity Mean (0-10)	3.3 (2.5) (n=95)	3.3 (2.5) (n=73)	3.3 (2.7) (n=22)
BPI General QOL Score Mean (questions 5a-5g) (0-10)	3.4 (3.0) (n=92)	3.4 (3.0) (n=71)	3.5 (3.1) (n=21)
BPI "Facial" Score Mean (questions 5h-5n) (0-10)	4.5 (3.3) (n=93)	4.7 (3.3) (n=71)	3.8 (3.3) (n=22)
HAD-A (0-21)	8.1 (4.8) (n=102)	8.1 (4.9) (n=77)	8 (4.6) (n=25)
HAD-D (0-21)	6.3 (4.4) (n=102)	6.1 (4.4) (n=77)	6.7 (4.7) (n=25)

Table 1. Group demographics and questionnaire statistics. BPI: Brief Pain Inventory, QOL: Quality of Life, HAD-A, HAD-D: Hospital Anxiety and Depression scale.

	Monotherapy			Polytherapy			Total		
	N	Dose range (mg)	Mean dose (mg) (SD)	N	Dose range (mg)	Mean dose (mg) (SD)	N	Dose range (mg)	Mean dose (mg) (SD)
CBZ	20	300-1800	820 (470)	8	400-1400	787 (422)	28	300-1800	810 (450)
OXC	30	70-1800	819 (457)	18	75-3600	1190 (894)	48	70-3600	958 (671)
LAM	9	25-800	311 (221)	19	50-1400	360 (311)	28	25-1400	344 (282)
GBP	12	200-3600	1875 (1332)	4	300-1800	1125 (665)	16	200-3600	1687 (1226)
PGB	7	150-600	353 (182)	4	150-700	437 (256)	11	150-700	384 (203)

Table 2. Group demographics and questionnaire statistics. BPI: Brief Pain Inventory, QOL: Quality of Life, HAD-A, HAD-D: Hospital Anxiety and Depression scale.

ABNAS toxic range cut-off score

The distributions of AEP and ABNAS scores in the entire patient group are shown in the histograms and boxplots below (Fig. 1). Scores have been converted to a 100-point scale, with zero and 100 being the lowest and highest possible scores of each questionnaire respectively. The histograms suggest that the distributions of both the AEP and ABNAS scores are not symmetrical. The scatterplot (lower right-hand Fig. 1) demonstrates that, as expected, there is a strong linear correlation between ABNAS and AEP total scores (Pearson's correlation coefficient: 0.67).

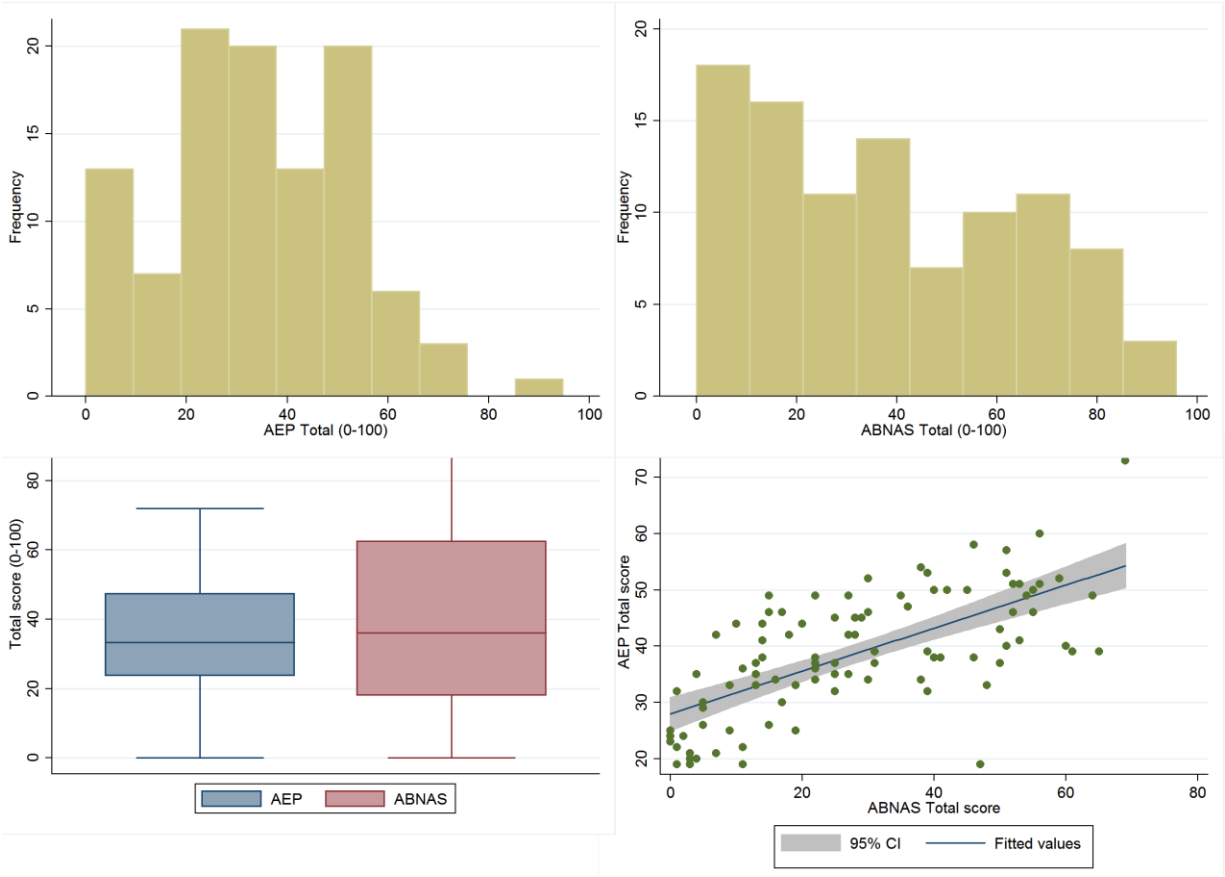


Figure 1. Histograms and boxplots of AEP and ABNAS scores in the entire patient group. Scores for these graphs have been converted to a 0-100 scale, with 0 and 100 being the lowest and highest possible scores in each test, respectively. Lower right hand

Out of the 104 patients that had filled in the AEP questionnaire, 30 fell into the toxic range, as defined by an AEP score higher than 45. In order to approximate a similar cut-off for the ABNAS questionnaire, we calculated the mean and standard error of the ABNAS score in this patient subgroup. We calculated the mean and corresponding 95% confidence interval as 43 (95% CI: 37.4 to 48.6). Fig. 2 shows boxplots of the ABNAS score, stratified by AEP score category (AEP 45 and AEP>45). A Mann-Whitney U test suggested a significant difference in ABNAS score between these groups (P-value < 0.001).

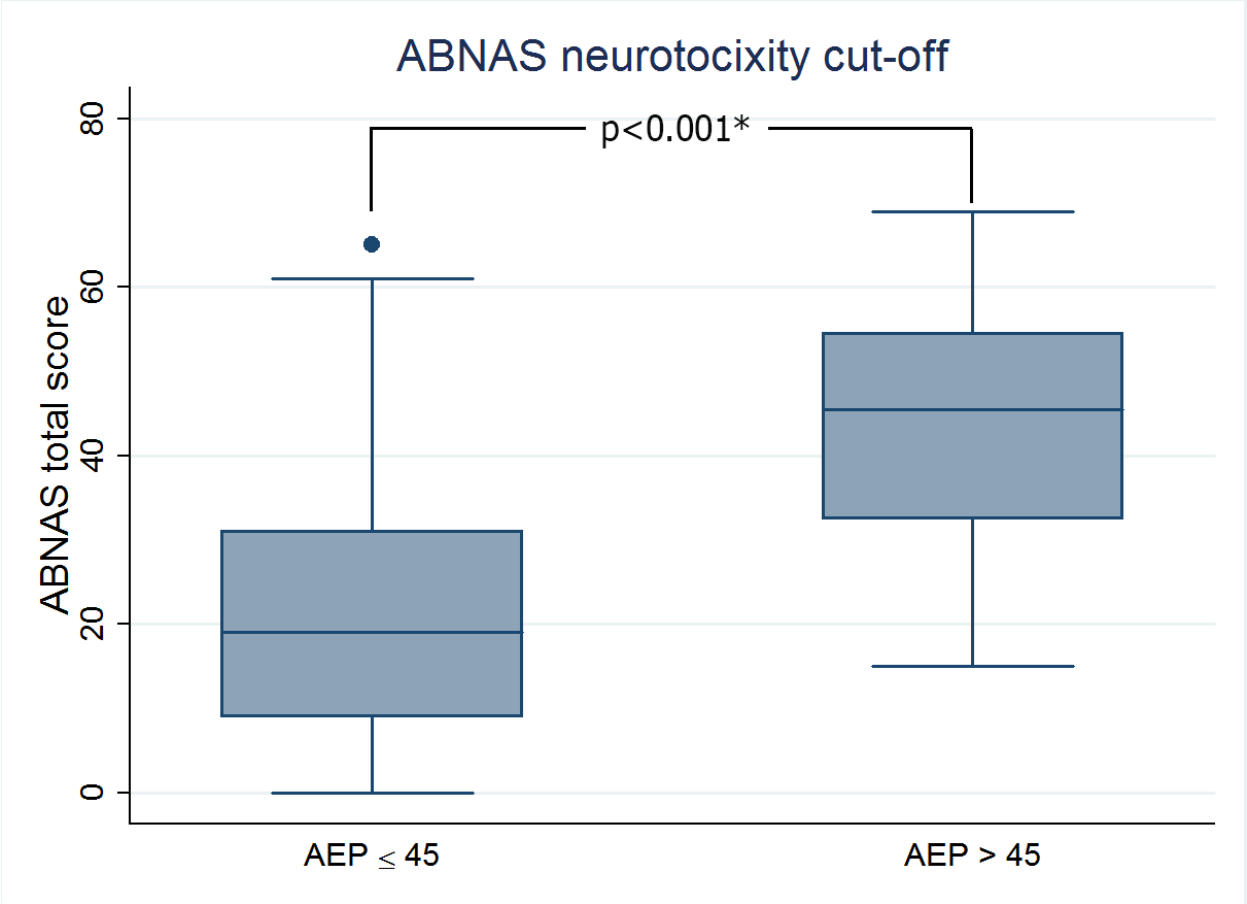


Figure 2. Boxplot of ABNAS total score in the two subgroups as defined by the AEP neurotoxicity cut-off score. (*Mann-Whitney U test)

ABNAS Subcategories, polytherapy, and dosage correlations

In terms of ABNAS sub-categories, the questions with highest scores were those in the categories of memory and cognition, while motor complaints were the least common (Fig. 3). It seems that distributions of score types are similar for carbamazepine and oxcarbazepine, with oxcarbazepine exhibiting lower scores in all categories (Fig. 3b). However, there is more variation for lamotrigine and gabapentin (although we note the small number of patients on each of these drugs). Comparing single and multiple drug groups (Fig. 3c) it looks like there might be lower scores in motor, and perhaps language, categories for the patients on single drugs compare to those on multiple drugs.

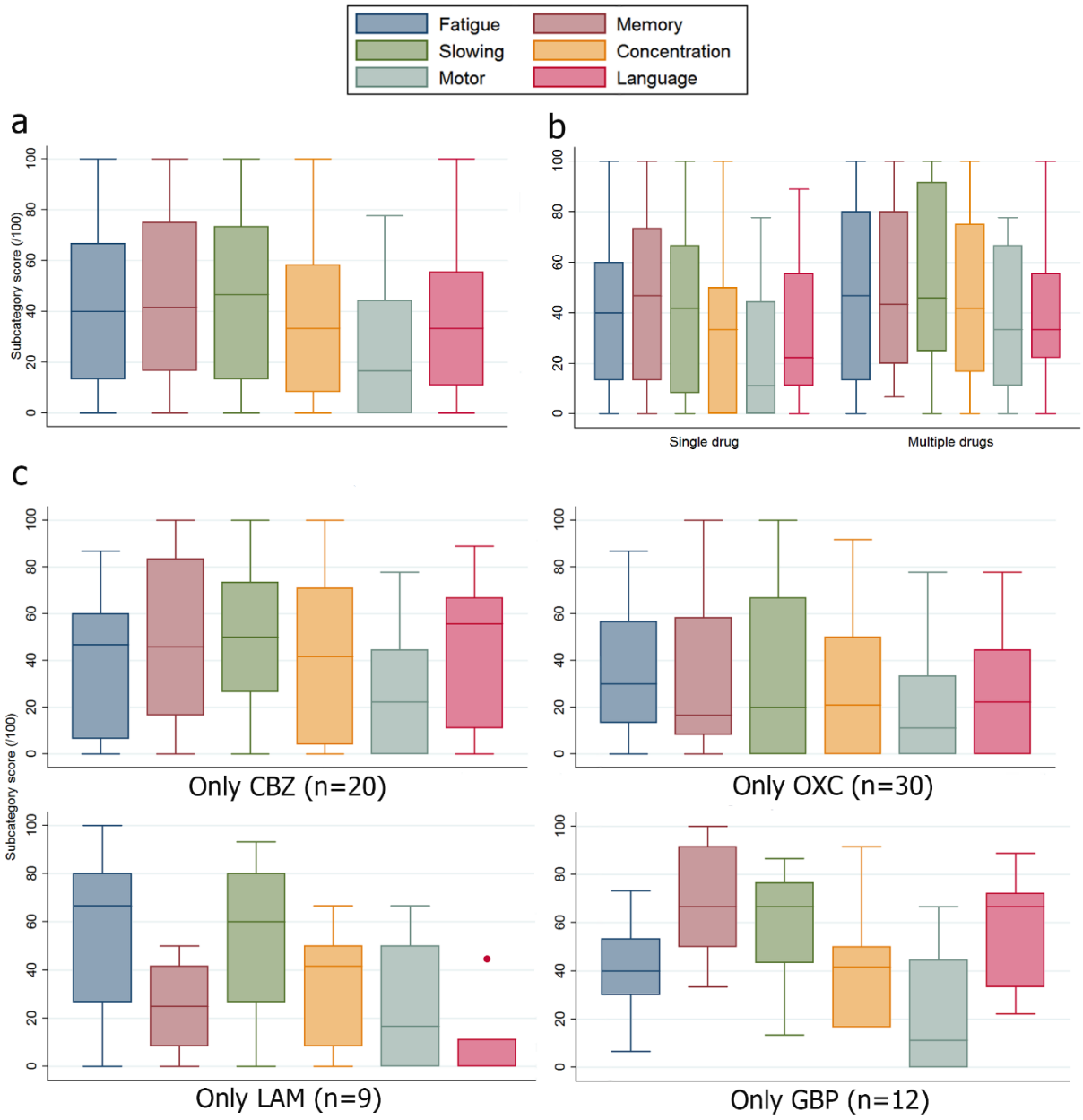


Figure 3. a) Boxplot of ABNAS subcategories scores in the entire patient group, converted to a 100-point scale (0 and 100 being the lowest and highest possible scores in each subcategory respectively. b) Boxplots of ABNAS subcategories for single drug gr

When comparing patients that were under a single drug medication with those taking two or more drugs, questionnaire scores tended to be lower for the single-drug group, a difference which was statistically significant in AEP total score (p=0.04), but only a trend in ABNAS total score (p=0.11)(two-sample t-test)(Supporting material Figure 4). 18 out of 78 monotherapy participants, and 12 out of 27

polytherapy participants were in the toxic dose range as defined by their AEP score. No statistically significant difference was evident when comparing these groups on BPI mean pain intensity (BPI questions 1-4). However, AEP and ABNAS total scores correlated positively with BPI mean pain intensity with a Spearman's rho of 0.4555 ($p<0.0001$) and 0.3372 ($p=0.0009$) respectively. In the polytherapy group, 12 patients had a mean BPI Pain score (questions 1-4) higher than 4, while 14 patients were below 4. One patient had not completed the BPI questionnaire.

Figure 4 shows plots of AEP, ABNAS and BPI (questions 1-4) scores versus drug dose for carbamazepine and oxcarbazepine. There are apparent positive linear correlations between AEP, ABNAS and BPI score and oxcarbazepine dose (right-side plots of Figures 4a, 4b)(Spearman's correlation coefficients: 0.54 for AEP, 0.46 for ABNAS, 0.18 for BPI). These linear correlations are much less apparent between AEP/ABNAS/BPI and carbamazepine dose (left-side plots of Fig. 4a, 4b)(Spearman's correlation coefficients: 0.24 for AEP, 0.13 for ABNAS, 0.06 for BPI). This could indicate some dose related side effects for oxcarbazepine. The apparent relationships and the disparity between the two drugs were still evident when using only participants on monotherapy.

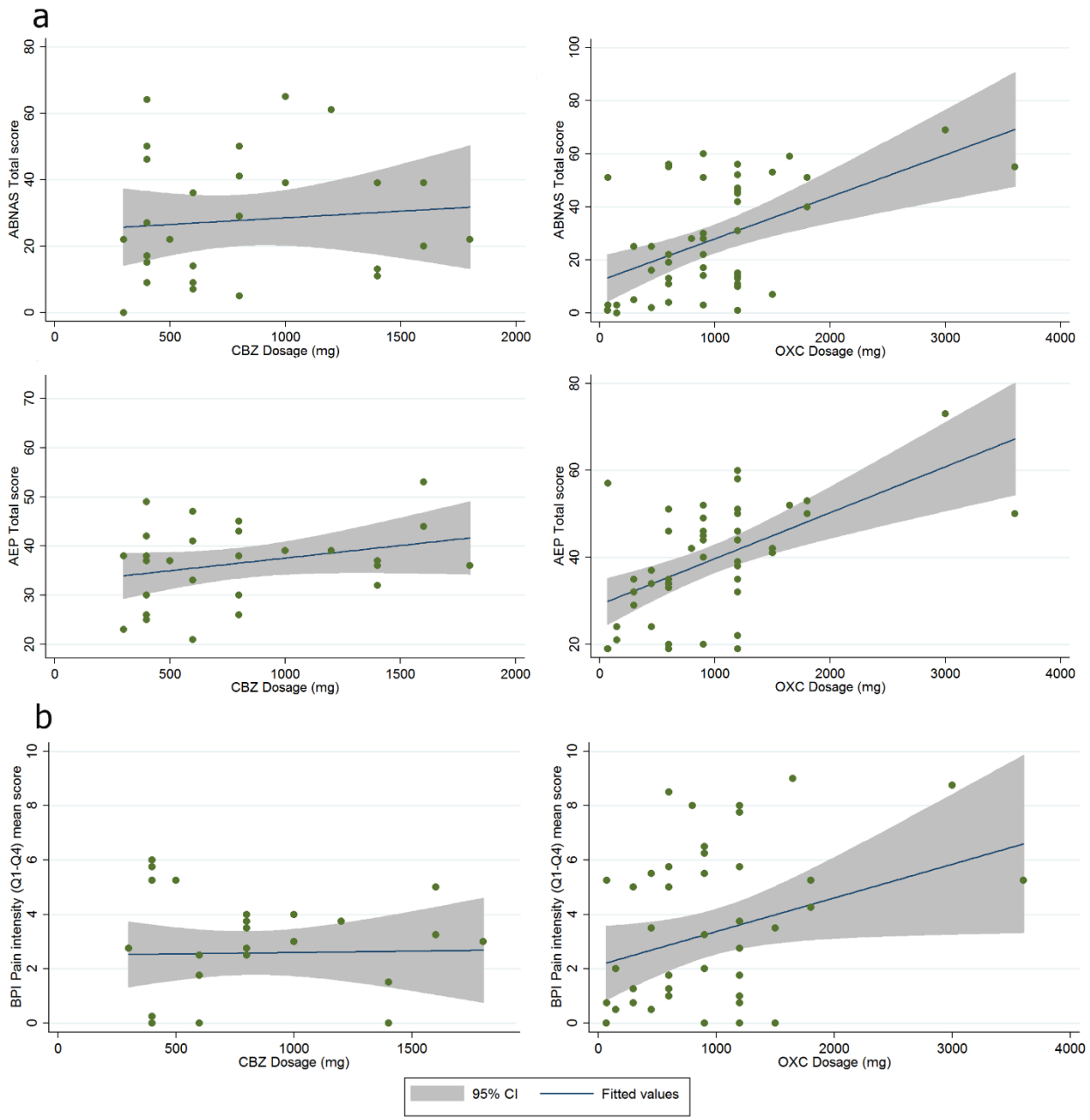


Figure 4. a) Scatterplots of questionnaire total scores against dosage of CBZ and OXC, with an approximated linear fit and 95% CI. Includes both monotherapy and polytherapy patients.

Qualitative comments

During the study patients were asked to offer comments on their opinion regarding all three questionnaires. Of 47 patients who commented, 23% preferred the AEP questionnaire, 66% the ABNAS and 11% had no preference. Patients who preferred the ABNAS questionnaire found the questions more

specific, so they felt sure they were interpreting them correctly. Several patients remarked that despite there being more questions in ABNAS, the overall time taken to fill in the entire questionnaire was shorter as they found that AEP had more general categories in comparison to ABNAS. Another difference noted by patients was that they felt the ABNAS questions purely allowed them to note their cognitive symptoms while the AEP had a more physical focus. Several patients commented that they found that cognitive symptoms were the most frequently experienced side effect, so they found the ABNAS questionnaire overall more relevant. However, this symptomatology could arise both due to the severity of the pain itself as well as anxiety and depression (30). Finally, the omission of any question addressing double vision in the ABNAS was also noted.

Regarding both questionnaires, in spite of patients being explicitly reminded to base their answers subjectively on medication adverse effects, several said they found it difficult to distinguish drug adverse effects with experiences caused by pain or concurrent medical conditions. Patients on multiple medications in particular had greater difficulty in completing the questionnaires. In one extreme case, a patient on 13 drugs was unable to complete any questions as she found it impossible to distinguish the effects of only her trigeminal neuralgia medication.

Patients responded positively to the aesthetics of the questionnaire and found both simple to interpret. Most patients did not have preference between a landscape or portrait questionnaire layout, though of the 17 that did state a preference, only one preferred a landscape setup. Reasons behind preferring a portrait layout were due to a dislike for visually scanning longer lines of text on the landscape layout.

Discussion

In the literature, guidelines or clinical protocols, major emphasis is put on drug efficacy and indications for their use, yet patient quality of life is often compromised by side effects. On the other hand, clinicians are provided with very little support when patients experience intolerability to a specific drug or treatment protocol. Very few randomized controlled trials use validated questionnaires of adverse events and the tendency is only to report significant ones (19).

This study shows that all current AEDs most commonly used in the management of TN and associated variants result in side effects. The most prominent ones are cognitive. We propose that ABNAS comes out as a comprehensive questionnaire in the clinical setting, when applied to TN and related patients. It supplements HAD-A and HAD-D to measure patients' quality of life and tolerability of treatment. However, these results alone are not enough to yet define a specific toxic range cut-off point, and more validation is required.

Some interesting findings arose when comparing different drugs' side effect profiles, the impact of each one's increase with dosage, and with polytherapy. Qualitatively, it seems that oxcarbazepine is better tolerated than carbamazepine in all categories of side effects. However, an increase in oxcarbazepine dosage was less tolerated, and correlated with higher side-effect scores. This was not the case with carbamazepine. Data was collected at least three months after treatment onset, so autoinduction of carbamazepine metabolism could be a possible reason for this observation, as it is not known to occur with oxcarbazepine. However, oxcarbazepine metabolites are very similar, and it is possible that this study's sample size is too small to pick up on such changes and subtle differences. Furthermore, without data on serum carbamazepine levels, which are unreliable, it was not possible to test this hypothesis in this study. One possible application of this observation could be that perhaps if a patient under carbamazepine treatment can tolerate its side effects, an increase in dosage could be attempted, with a

potential for side effects to remain at the same level. The same cannot be easily said about oxcarbazepine based on our results.

In terms of side effect sub-groups, lamotrigine and oxcarbazepine seem to have the lowest negative impact on memory. If fatigue is a problem, oxcarbazepine and pregabalin may prove a better option. Interestingly in 528 patients using pregabalin for anxiety or panic disorders, the major side effects were dizziness, insomnia for 9% and somnolence in 8.5% (31). These were not measured with a questionnaire but through self-reporting, with 77% experienced at least one side effect. Finally, our results suggest that when comparing multiple medications with a single agent, there is a tendency for the side effects to increase, particularly in the subcategories of concentration, motor coordination, and language, but with low statistical significance.

As these self-complete questionnaires can be filled out in the waiting room prior to consultation, they can provide a better, patient-centered management without necessarily expecting an increase in consultation time. They can lead to further laboratory investigations, be used to monitor side effects over time, and determine which drug and dosage is better suited for each patient. Potentially they could prompt to a switch to other drugs, and/or initiate polytherapy or referral for neurosurgical therapies.

Limitations

The nature of self-reporting is one of the main limitations of this study, as is often the case with questionnaire research. Pain, well known to being a subjective and therefore complex experience, often influences the reported side effects of medications. Some patients do find difficult to differentiate between symptoms linked with pain of underlying disease, mood, and or medications' side effects, as is evident by the correlation we found between AEP/ABNAS total scores and BPI mean pain intensity. For example, "trouble in their mouth", could be to both the condition itself as well as development of the side effect. Depression and anxiety are also known to influence response to treatment and can

confound results. Finally, the sample population is lacking in homogeneity. Future studies in the topic will greatly benefit from recruiting a more homogeneous group of patients.

Future directions

Subjectively, our dataset has shown the importance of assessing cognitive functions in patients who are often performing highly complex tasks in their demanding professional lives. It would therefore be important to also develop objective tests using computer-based programs to measure these effects e.g. the Kinematic Assessment Tool (KAT). The KAT is a computerized battery of psychometric tests. Information is acquired via a touch-sensitive screen and in addition may also pick up further side effects such as unsteadiness or tremor (32). Furthermore, the ABNAS questionnaire would also be a useful tool in future studies comparing side effect profiles of centrally and peripherally acting medications.

Conclusion

The ABNAS questionnaire can be a useful tool for monitoring side effects and personalizing treatment, as it depicts patients' side effect profile in more detail, and is better focused on common cognitive adverse effects than the questionnaires commonly used today. The present study attempted to quantify side effects more objectively so that clinicians were alerted to switch pharmacotherapy from one agent to another or even to consider surgical solutions as last resort. Polytherapy showed increase in both number and intensity of side effects. Although CBZ and OXC seem to share similar side effect profiles, patients under OXC tended to report less side effects at low dose. However, these seemed to be dose-dependent, than CBZ. ABNAS data also allowed for a more accurate depiction of the types of side effects associated with each drug, through subcategory scores. Evidently, more research is needed to further validate ABNAS total score and sub-scores as measures of interest, but it could prove advantageous over AEP in similar patient groups to the present. Future research could also incorporate ABNAS and data similar to this study to investigate side effects and quality of life comparing medical and surgical treatments.

Conflict of Interest: JZ is has a consultancy with Biogen.

Acknowledgements: This project was supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre. RC and JZ undertook this work at UCL/UCLHT who received a proportion of funding from the Department of Health's NIHR Biomedical Research Centre funding scheme. This paper began as a project coordinated by the Academics organization, which facilitated the placements of then students, VT, GL, and JR.

Funding: No grant or other particular source of funding.

Ethical approval: Patients all sign a general consent form for their data to be used for research and all complete these questionnaires as routine at all appointments except for ABNAS for which verbal consent was acquired.

References:

(1) IHS. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia : an international journal of headache 2013; 33: 629-808.

(2) LAMBRU G, MATHARU MS. SUNCT, SUNA and trigeminal neuralgia: different disorders or variants of the same disorder? Current opinion in neurology 2014; 27: 325-31.

(3) GRONSETH G, CRUCCU G, ALKSNE J, et al. Practice parameter: the diagnostic evaluation and treatment of trigeminal neuralgia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the European Federation of Neurological Societies. Neurology 2008; 71: 1183-90.

(4) ZAKRZEWSKA JM, CHAUDHRY Z, NURMIKKO TJ, PATTON DW, MULLENS EL. Lamotrigine (lamictal) in refractory trigeminal neuralgia: results from a double-blind placebo controlled crossover trial. Pain 1997; 73: 223-30.

(5) KHAN OA. Gabapentin relieves trigeminal neuralgia in multiple sclerosis patients. Neurology 1998; 51: 611-4.

(6) OBERMANN M, YOON MS, SENSEN K, MASCHKE M, DIENER HC, KATSARAVA Z. Efficacy of pregabalin in the treatment of trigeminal neuralgia. Cephalalgia : an international journal of headache 2008; 28: 174-81.

(7) FROMM GH, TERRENCE CF, CHATTHA AS. Baclofen in the treatment of trigeminal neuralgia: double-blind study and long-term follow-up. Annals of neurology 1984; 15: 240-4.

(8) BENNETTO L, PATEL NK, FULLER G. Trigeminal neuralgia and its management. BMJ (Clinical research ed) 2007; 334: 201-5.

(9) DI STEFANO G, LA CESA S, TRUINI A, CRUCCU G. Natural history and outcome of 200 outpatients with classical trigeminal neuralgia treated with carbamazepine or oxcarbazepine in a tertiary centre for neuropathic pain. The journal of headache and pain 2014; 15: 34.

(10) SPATZ AL, ZAKRZEWSKA JM, KAY EJ. Decision analysis of medical and surgical treatments for trigeminal neuralgia: how patient evaluations of benefits and risks affect the utility of treatment decisions. Pain 2007; 131: 302-10.

(11) ZAKRZEWSKA JM. Consumer views on management of trigeminal neuralgia. Headache 2001; 41: 369-76.

(12) WIFFEN PJ, DERRY S, MOORE RA, MCQUAY HJ. Carbamazepine for acute and chronic pain in adults. The Cochrane database of systematic reviews 2011: Cd005451.

(13) MOORE RA, STRAUBE S, WIFFEN PJ, DERRY S, MCQUAY HJ. Pregabalin for acute and chronic pain in adults. The Cochrane database of systematic reviews 2009: Cd007076.

(14) WIFFEN P, COLLINS S, MCQUAY H, CARROLL D, JADAD A, MOORE A. Anticonvulsant drugs for acute and chronic pain. The Cochrane database of systematic reviews 2005: Cd001133.

(15) WIFFEN PJ, DERRY S, MOORE RA. Lamotrigine for acute and chronic pain. The Cochrane database of systematic reviews 2011: Cd006044.

(16) WIFFEN PJ, REES J. Lamotrigine for acute and chronic pain. The Cochrane database of systematic reviews 2007: Cd006044.

(17) ZHANG J, YANG M, ZHOU M, HE L, CHEN N, ZAKRZEWSKA JM. Non-antiepileptic drugs for trigeminal neuralgia. The Cochrane database of systematic reviews 2013; 12: Cd004029.

(18) YANG M, ZHOU M, HE L, CHEN N, ZAKRZEWSKA JM. Non-antiepileptic drugs for trigeminal neuralgia. The Cochrane database of systematic reviews 2011: Cd004029.

(19) HOFFER D, SMITH SM, PARLOW J, ALLARD R, GILRON I. Adverse event assessment and reporting in trials of newer treatments for post-operative pain. Acta anaesthesiologica Scandinavica 2016; 60: 842-51.

(20) PANELLI RJ, KILPATRICK C, MOORE SM, MATKOVIC Z, D'SOUZA WJ, O'BRIEN TJ. The Liverpool Adverse Events Profile: relation to AED use and mood. Epilepsia 2007; 48: 456-63.
(21) GILLIAM FG, FESSLER AJ, BAKER G, VAHLE V, CARTER J, ATTARIAN H. Systematic screening allows reduction of adverse antiepileptic drug effects: a randomized trial. Neurology 2004; 62: 23-7.
(22) BESI E, BONIFACE DR, CREGG R, ZAKRZEWSKA JM. Comparison of tolerability and adverse symptoms in oxcarbazepine and carbamazepine in the treatment of trigeminal neuralgia and neuralgiform headaches using the Liverpool Adverse Events Profile (AEP). The journal of headache and pain 2015; 16: 563.
(23) BROOKS J, BAKER GA, ALDENKAMP AP. The A-B neuropsychological assessment schedule (ABNAS): the further refinement of a patient-based scale of patient-perceived cognitive functioning. Epilepsy research 2001; 43: 227-37.
(24) ALDENKAMP AP, VAN MEEL HF, BAKER GA, BROOKS J, HENDRIKS MP. The A-B neuropsychological assessment schedule (ABNAS): the relationship between patient-perceived drug related cognitive impairment and results of neuropsychological tests. Seizure 2002; 11: 231-7.
(25) MAARBJERG S, GOZALOV A, OLESEN J, BENDTSEN L. Concomitant persistent pain in classical trigeminal neuralgia--evidence for different subtypes. Headache 2014; 54: 1173-83.
(26) CHARLESTON LT. Do trigeminal autonomic cephalalgias represent primary diagnoses or points on a continuum? Current pain and headache reports 2015; 19: 22.
(27) PALIWAL VK, UNIYAL R, GUPTA DK, NEYAZ Z. Trigeminal neuralgia or SUNA/SUNCT: a dilemma unresolved. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology 2015; 36: 1533-5.
(28) SANDHU SK, HALPERN CH, VAKHSHORI V, MIRSAEEDI-FARAHANI K, FARRAR JT, LEE JY. Brief pain inventory--facial minimum clinically important difference. Journal of neurosurgery 2015; 122: 180-90.
(29) LEE JY, CHEN HI, URBAN C, et al. Development of and psychometric testing for the Brief Pain Inventory-Facial in patients with facial pain syndromes. Journal of neurosurgery 2010; 113: 516-23.
(30) ZIGMOND AS, SNAITH RP. The hospital anxiety and depression scale. Acta psychiatrica Scandinavica 1983; 67: 361-70.
(31) MONTGOMERY S, EMIR B, HASWELL H, PRIETO R. Long-term treatment of anxiety disorders with pregabalin: a 1 year open-label study of safety and tolerability. Current medical research and opinion 2013; 29: 1223-30.
(32) CULMER PR, LEVESLEY MC, MON-WILLIAMS M, WILLIAMS JH. A new tool for assessing human movement: the Kinematic Assessment Tool. Journal of neuroscience methods 2009; 184: 184-92.

Supporting material

Supporting material Figure 1. The AEP questionnaire

ADVERSE EVENTS PROFILE

During the past four weeks, have you had any of the problems or side-effects listed below?

For each item, if it has always or often been a problem, circle 4; if it has sometimes been a problem, circle 3; and so on. Please be sure to answer every item

	Always a problem	Sometimes a problem	Rarely a problem	Never a problem
Unsteadiness	4	3	2	1
Tiredness	4	3	2	1
Restlessness	4	3	2	1
Feelings of aggression	4	3	2	1
Nervousness and/or aggression	4	3	2	1
Headache	4	3	2	1
Hair loss	4	3	2	1
Problems with skin, e.g. acne, rash	4	3	2	1
Double or blurred vision	4	3	2	1
Upset stomach	4	3	2	1
Difficulty in concentrating	4	3	2	1
Trouble with mouth or gums	4	3	2	1
Shaky hands	4	3	2	1
Weight gain	4	3	2	1
Dizziness	4	3	2	1
Sleepiness	4	3	2	1
Depression	4	3	2	1
Memory Problems	4	3	2	1
Disturbed sleep	4	3	2	1

Supporting material Figure 2. The ABNAS questionnaire

A-B NEUROPSYCHOLOGICAL ASSESSMENT SCHEDULE

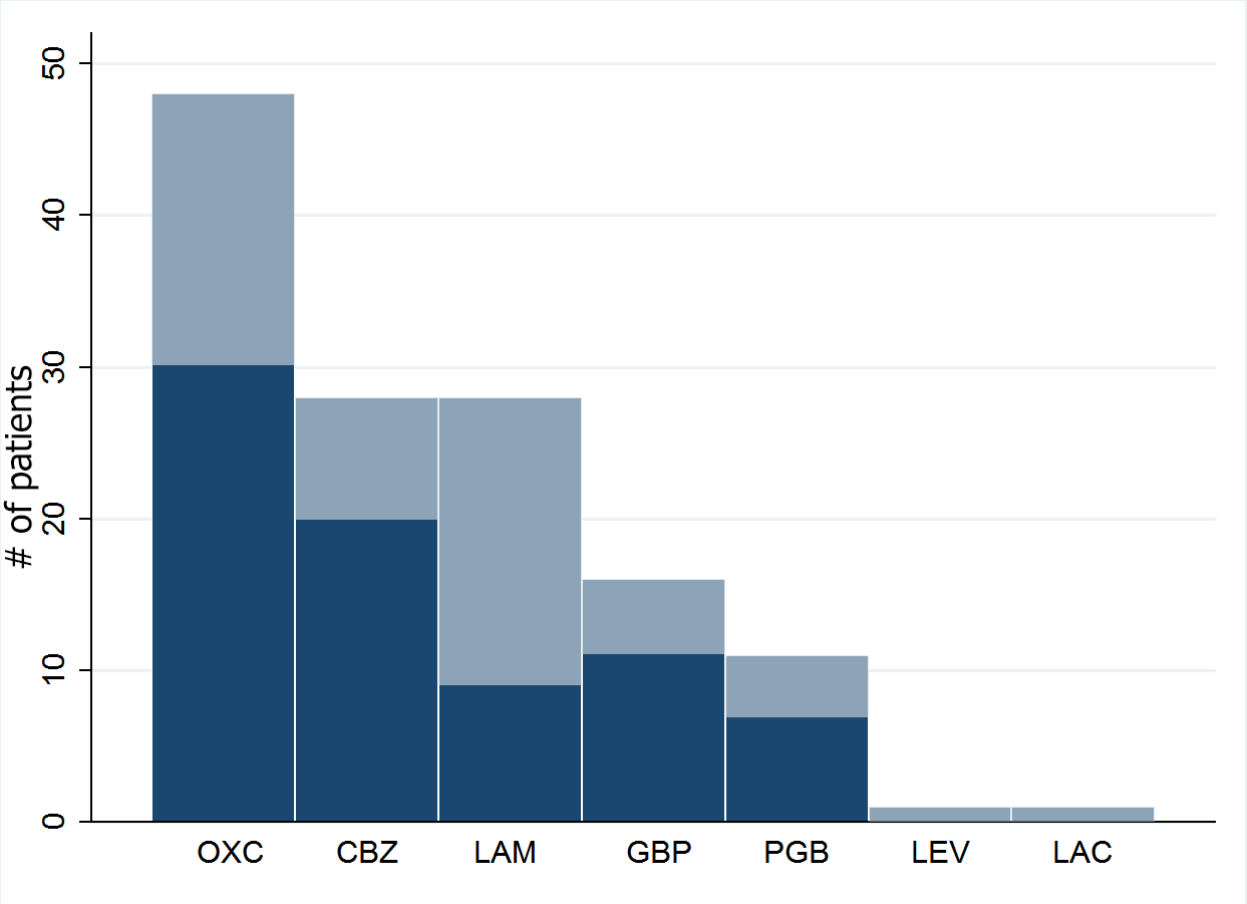
Below is a list of problems people sometimes have with the medicines they take for their pain.
Have you any problems listed which you think may have been caused by the drugs you take?

For each item, if it is not a problem ring 0; if it is a mild problem ring 1; if it is a moderate problem ring 2; if it is a serious problem ring 3.

Item	No problem	A Mild Problem	A Moderate Problem	A Serious Problem
I am less enthusiastic about day to day activities	0	1	2	3
My mind does not work as fast as it should	0	1	2	3
I have difficulties remembering names of people	0	1	2	3
I have difficulties following a book or a film	0	1	2	3
I feel clumsy	0	1	2	3
I have problems finding the correct word	0	1	2	3
I am less capable of undertaking initiatives	0	1	2	3
My thinking has slowed down	0	1	2	3
I forget things e.g. an appointment or where I put an object	0	1	2	3
I have difficulties concentrating on the thing I am doing	0	1	2	3
I cannot use a pen or pencil accurately	0	1	2	3
I have problems understanding what I read	0	1	2	3
I tire easily and have little energy	0	1	2	3
It takes me longer to do day to day things	0	1	2	3
I forget things that people have said to me	0	1	2	3
I cannot concentrate for more than a short period of time	0	1	2	3
I constantly bump against tbales, doorposts, etc.	0	1	2	3
I feel worn out	0	1	2	3
It costs more time for me to get started	0	1	2	3
I get confused and forget what I was doing	0	1	2	3
I get distracted more easily	0	1	2	3
I sometimes stutter or am unable to find the correct words	0	1	2	3
I feel I react too slowly to things that are said to me	0	1	2	3
I cannot keep an activity going for long	0	1	2	3

Supporting material Figure 3. Bar chart indicating number of patients that were under medication with each drug. Darker hue indicates monotheraphy, lighter hue indicates part of polytherapy. OXC: Oxcarbazepine CBZ: Carbamazepine LAM: Lamotrigine GBP: Gabapentin PGB:

Pregabalin LEV: Levetiracetam LAC: Lacosamide



Supporting material Figure 4. Box-plot Comparison of questionnaire scores between subgroups of patients under single and multiple drug regimens. (* two-sample t-test)