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Characterizing Treatment Utilization Patterns for Trigeminal Neuralgia in the United States

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Abstract

Background and aim: Trigeminal neuralgia (TN) is a rare orofacial disorder characterized by severe unilateral paroxysmal pain in the region of the fifth cranial nerve. Clinical guidelines recommend carbamazepine (only US Food and Drug Administration–approved drug for TN) and oxcarbazepine as first-line therapies. We utilized the US Truven Health MarketScan® database to examine treatment patterns among patients with TN.

Methods: Included patients were aged ≥18 years, newly diagnosed with TN (≥2 TN diagnoses ≥14 days apart; no diagnosis in the prior year), continuously enrolled 1 year pre-index, with ≥3 years' follow-up post-index. We assessed utilization of selected pharmacotherapies (carbamazepine, oxcarbazepine, pregabalin, gabapentin, baclofen, duloxetine, topiramate), surgery (posterior fossa, radiosurgery), and injections (peripheral anesthetic injections, Gasserian ganglion procedures) for TN.

Results: 3685 patients were included (2425 commercial, 1260 Medicare; 71.8% female; mean[SD] age, 59[15] years). Overall, 72.5% of patients received at least 1 studied medication, most commonly carbamazepine (51.7%) or gabapentin (48.6%). Sixty-five percent of pharmacologically treated patients had ≥2 treatment episodes; 41.6% had ≥3 (defined by a change in pharmacotherapy [monotherapy/combination] regimen). Overall, 12.3% had surgery and 7.3% injections; 42.9% received opioids for TN.

Conclusions: In the 3 years after diagnosis, patients with TN in the United States receive a variety of pharmacological treatments, including opioids, despite carbamazepine being the only approved medication. A notable proportion utilize surgeries/injections. A high proportion of pharmacologically treated patients receive multiple treatment episodes, suggesting frequent therapy switching, perhaps due to suboptimal efficacy/tolerability. Our data suggest a high burden of illness associated with TN.

Keywords [3 to 5 per journal guidelines]

Trigeminal neuralgia; pharmacological treatment; surgery; treatment patterns; claims analysis

INTRODUCTION

Trigeminal neuralgia (TN) is an orofacial pain disorder characterized by severe shock-like recurrent pain occurring within the region of the fifth cranial nerve.[1] The condition is considered rare, with estimates for annual incidence ranging from 4.7 to 28.9 per 100,000 persons.[2-5] However, the patient burden of TN is substantial owing to the severity of the pain, which may worsen or become more prolonged over time.[6,7] In one study, almost 60% of patients scored the intensity of TN paroxysmal stabbing pain as "the worst possible pain."[8] There is evidence that TN-associated pain can lead to disability, depression, and anxiety, having a significant impact on patient's quality of life, as well as indirect costs to society resulting from work absenteeism.[6,7]

Clinical guidelines recommend carbamazepine, the only medication currently approved by the US Food and Drug Administration (FDA) for TN, and oxcarbazepine (a keto-analog of carbamazepine), both anticonvulsants, as first-line treatments for TN.[9] While there is evidence to support the use of carbamazepine for pain relief in TN (number need to treat [NNT] of 2)[10], its use must be considered in light of a poor tolerability profile and adverse effects that can include dizziness, liver damage, and cognitive impairment (number needed to harm for carbamazepine withdrawal of 24, 95% CI 14 –112).[10,11,12-16] Further, caution is recommended in patients with comorbidities due to the potential for drug interactions.[17] Oxcarbazepine has greater tolerability and a reduced risk of drug interactions than carbamazepine, but its efficacy has not been confirmed in well-conducted randomized controlled trials.[10] Other pharmacological treatments used in clinical practice for TN and neuropathic pain conditions include the anticonvulsants gabapentin (NNT of 8.0 in postherpetic neuralgia and NNT of 5.9 in painful diabetic neuropathy),[18] pregabalin (combined NNT of 4.2 in post-herpetic neuralgia and painful diabetic neuropathy),[19] lamotrigine (NNT of 2.1 in TN as an add-on treatment),[20] and topiramate (NNT of 7.4 in

painful diabetic neuropathy);[19] the skeletal muscle relaxant baclofen (NNT of 1.4);[20] and the selective serotonin reuptake inhibitor duloxetine; however, these treatments are not specifically indicated for TN and the evidence for their use in treating representative TN patient populations is limited.[9,10,21-23] Previous studies have reported that not all patients with TN receive pharmacological treatment, but that among treated patients, carbamazepine was the most frequently prescribed first-line drug for TN in the United Kingdom and the Netherlands.[5,24]

Guidelines recommend that surgery should be considered for patients refractory to medical treatment,[9] as indicated by increased likelihood of receiving ≥2 pharmacological treatments.[25] Surgical procedures used for TN treatment in clinical practice include percutaneous procedures on the Gasserian ganglion, stereotactic radiosurgery, and microvascular decompression.[9,10,23] However, high-quality evidence to support and guide best practice remains limited. Additionally, recent studies have suggested that botulinum toxin (Botox, Allergan, Irvine, CA) may have some efficacy in the treatment of TN pain.[26] Peripheral nerve injections (distal to the Gasserian ganglion), including local anesthetics or neurolytic agents such as alcohol, are also sometimes used, but evidence for their efficacy is either negative or insufficient.[9] While opioids are commonly used in clinical practice to treat severe pain,[27] there is a lack of evidence on the efficacy of opioids to treat TN-related pain, and a Cochrane review has highlighted uncertainty regarding the use of opioids for neuropathic pain in general, owing to limited evidence as well as concerns about addiction and side effects.[28] Of note, opioid abuse is considered a growing epidemic in the United States, leading the FDA to develop an action plan to reduce the impact of such abuse.[29]

Given the absence of high-quality evidence, treatment approaches for TN vary, and real-world treatment patterns among patients with TN are poorly understood. An improved understanding of the treatment of TN in clinical practice may help to identify unmet needs

within this population and inform health care decision making. We therefore undertook a retrospective claims database analysis to examine the real-world pharmacological and nonpharmacological treatment patterns among a cohort of patients newly diagnosed with TN enrolled in commercial and Medicare managed care or supplemental health insurance plans in the United States.

METHODS

Study Design and Data Source

This was a retrospective analysis utilizing claims data from the Truven Health MarketScan® (Truven Health, Ann Arbor, MI) commercial and Medicare claims databases, from 2010 to quarter 3 2015. The databases contain administrative claims and eligibility records for >100 million commercially insured individuals and 8 million Medicare beneficiaries from all regions in the United States. These include medical services claims (excluding dental) in inpatient and outpatient settings, with associated procedures and diagnosis codes, which have been submitted for reimbursement. They also contain information on pharmacy dispensing claims, as well as demographic information including age, sex, health plan type, and region of residence. Commercial plans in MarketScan are typically employer sponsored to cover employees and their dependents, while Medicare is government funded and includes patients ≥65 years of age. Medicare enrollees in MarketScan are covered by Medigap or Medicare Managed Care Plans (eg, Medicare Advantage Plans), which generally include benefits that Original Medicare does not cover (such as copayments, deductibles, and prescription drug coverage). The databases are compliant with the Health Insurance Portability and Accountability Act, and all data are deidentified.

Patient Population

Patients were included in the analysis if they were ≥18 years of age and newly diagnosed with TN during the study period. Patients were required to have ≥2 claims with a

TN diagnosis code (International Classification of Diseases, Ninth Revision (ICD-9) 350.1, 350.8; ICD10 G500) that were dated ≥14 days apart. The date of the first claim was designated as the index date. Newly diagnosed patients were defined as those without a diagnosis for TN in the year before index. Patients also had to be continuously enrolled for 1 year pre index, and have ≥3 years' follow-up post index, to ensure a sufficient duration to capture treatment patterns and switching over time (Fig. 1).

Outcome Measures

Patient Demographics and Comorbidities

Demographic information was collected at the index date (first TN claim). Comorbidities, including other chronic pain conditions, were based on specified diagnosis codes associated with claims in the 1 year before index (listed in Table, Supplemental Digital Content 1, http://links.lww.com/CJP/A478).

Pharmacological Treatments

We evaluated the utilization of pharmacological treatments based on prescription fills over the 3 years on or post index. The following 7 pharmacological treatments were considered medications of interest, and were identified in the database by National Drug Codes: carbamazepine, oxcarbazepine, pregabalin, gabapentin, baclofen, duloxetine, and topiramate. These pharmacological treatments were identified as commonly used for TN treatment in clinical practice, based on clinical experience and overall volume of prescriptions for newly diagnosed patients with TN in the database. Because outpatient pharmacy claims do not include diagnosis information, in order to attribute prescription fills to the management of TN, there had to be a medical claim with a TN diagnosis up to 30 days before or 7 days after the first prescription fill for each of the 7 medications. Subsequent prescription fills of the same medication were not required to have a medical claim with a TN

diagnosis, because patients can typically receive a supply of (nonopioid) medications for up to 12 months without a face-to-face physician consultation (ie, no medical claim for TN).

The frequency of change of pharmacological treatments was evaluated according to treatment episodes (based on analysis of the 7 medications of interest listed above, and excluding opioid use). A treatment episode was defined as any unique pharmacological treatment regimen (monotherapy or combination), with the end of each episode defined by a change in regimen (add-on, switch, or discontinuation; for definitions see Table, Supplemental Digital Content 2, http://links.lww.com/CJP/A479). Discontinuation was defined as a >90-day gap in supply; a 90-day gap was required to ensure true discontinuation versus extension of the supply due to missed doses, and is consistent with the definition of discontinuation used in other claims analyses.[30-34]

Surgery and Injections

Utilization of nonpharmacological treatments, in the form of surgery and injections, was evaluated over the 3 years post index. Surgeries and injections were identified by unique procedure codes (Table, Supplemental Digital Content 3, http://links.lww.com/CJP/A480). Surgery included posterior fossa surgery (eg, microvascular decompression) and radiosurgery, while injections included peripheral anesthetic injections and ablative procedures at the Gasserian ganglion level. Botulinum toxin was captured under peripheral anesthetic injections. The surgeries and injections of interest were selected as being used for the treatment of TN in clinical practice, based on clinical experience and review of the literature.[35,36] To be included in the analysis, the surgeries and injections were required to have a TN diagnosis in one of the diagnosis fields (primary diagnosis of TN for inpatient claims, or any TN diagnosis for outpatient claims).

Opioids

Patterns of opioid use were assessed, but were not included for the analysis of treatment episodes because opioids are not considered to be a standard-of-care maintenance treatment for TN, and effectiveness in other neuropathic pain conditions is uncertain. To be considered TN related, there had to be a medical claim with a TN diagnosis up to 30 days before or 7 days after any opioid prescription fill. Because opioids are commonly used to treat pain conditions other than TN, we required that all opioid fills be associated with a TN medical claim (in contrast to only the first fill for other medications).

All analyses were reported for all eligible patients and stratified by insurance type (commercial vs. Medicare) in order to take into account the age difference between the 2 populations, which has an implication for comorbidities and treatment patterns, and because the overall age distribution is not representative of the general US population (the Medicare population in the Truven Health MarketScan database accounts for only a small proportion of those ≥65 years of age). However, reporting of data in the text is for the combined overall population, except in cases where there were notable differences between groups. All data are reported as descriptive statistics.

RESULTS

Patient Population

A total of 3685 patients were included in the analysis, of whom 2425 were enrolled in commercial plans, and 1260 in Medicare plans (Fig. 1).

Demographics and Comorbidities

Mean (SD) age at first TN diagnosis was 59.0 (15.3) years for the overall population; 71.8% of patients were female (Table 1). As expected, owing to differences in the age of the populations, the proportions of patients with cerebrovascular disease, hypertension, and diabetes were higher in the Medicare than the commercial population. The proportion with multiple sclerosis (MS) was higher in the commercial population. Among the most common

pain comorbidities, osteoarthritis, low back pain, and stroke-associated pain were more frequent in the Medicare population, while migraine and fibromyalgia were more frequent among commercial patients. The highest proportion of the overall patient population lived in the south, with a higher proportion of commercial than Medicare patients. The proportion of patients living in North Central was higher among the Medicare population. Overall, the lowest proportion of patients lived in the west. (Table 1).

Overall Pharmacological and Non-pharmacological Treatment Utilization

Overall, almost three-quarters of patients received ≥1 pharmacological treatment, surgery, or injection of interest during the 3 years following TN diagnosis (a quarter had a diagnosis of TN, but received none of the pharmacological or nonpharmacological treatments of interest during the study period; Table 2). The majority (84.4%) of treated patients received pharmacological monotherapy as their first treatment; 12.0% were treated first with combination pharmacological therapy (ie, polypharmacotherapy) and 3.6% with surgery (posterior fossa surgery or radiosurgery). For the second and third treatments, the proportions with polypharmacy and surgery increased, while monotherapy decreased (Table, Supplemental Digital Content 5, http://links.lww.com/CJP/A482).

Pharmacological Treatment

Almost three-quarters of patients received pharmacological treatment during the first 3 years, with over one-third receiving ≥2 medications of interest, and a notable proportion receiving ≥3 medications of interest. Almost one-third of the study population added or switched treatment during the 3 years following diagnosis (Table 2). Among patients who received pharmacological treatments, around two-thirds (64.5%) had ≥2 treatment episodes, while 41.6% had ≥3 episodes (Table, Supplemental Digital Content 6, http://links.lww.com/CJP/A483).

Fewer patients received pharmacological treatment in the second and third years following diagnosis (48.4% and 44.4%, respectively) than in the first year (70.2%), and a smaller proportion of those treated had multiple episodes of treatment (Table, Supplemental Digital Content 7, http://links.lww.com/CJP/A484).

Carbamazepine was received by around half (51.7%) of pharmacologically treated patients, while just under half (48.6%) received gabapentin. Just under a quarter received pregabalin (23.1%), with a slightly smaller proportion receiving oxcarbazepine (21.3%). The other medications (baclofen, duloxetine, and topiramate) were each used by ~10% of the overall population; use of these medications was higher among commercial than Medicare patients (Fig. 2).

Among those who started treatment with a pharmacological monotherapy, carbamazepine was the most commonly received drug, although only a slightly smaller proportion were prescribed gabapentin first line (Table 3). For the most frequently used first-line monotherapies (carbamazepine, gabapentin, oxcarbazepine, and pregabalin), the duration of treatment (from initiation until regimen change) was generally similar among the medications (median, ~90 days); median duration tended to be longer for Medicare than commercial patients, although means were more similar (Table 3).

Carbamazepine and gabapentin were also the most frequently prescribed second- and third-line pharmacological monotherapies. Duration of second-line monotherapy was generally similar to first line, while third-line monotherapy tended to be shorter in duration (Tables, Supplemental Digital Content 8, http://links.lww.com/CJP/A485 and 9, http://links.lww.com/CJP/A486).

Analysis of treatment switch patterns indicated that patients are most likely to switch across classes of therapy, from carbamazepine/oxcarbazepine to pregabalin/gabapentin, and vice versa (Figure, Supplemental Digital Content 10, http://links.lww.com/CJP/A487).

Surgeries and Injections

Among patients who received a medication of interest before first surgery, the median duration, from starting pharmacological treatment until first surgery, was 224 (mean, 322) days. The duration was longer for commercial than Medicare patients (Table, Supplemental Digital Content 11, http://links.lww.com/CJP/A488).

The majority of patients who had posterior fossa surgery (96.4%), radiosurgery (76.6%), and ablative procedures at the Gasserian ganglion (72.8%) had only 1 such episode of treatment. The majority receiving peripheral anesthetic injections (55.6%) had ≥2 injections (Fig. 3).

Among patients who received surgery during the 3 years following diagnosis, most received ≥1 pharmacological treatment before first surgery. A sizeable minority received no pharmacological treatments before first surgery, a large proportion of whom (n=81/98) did not receive the studied pharmacological treatments at all during the study period (Table 4). After first surgery, almost three-quarters of patients received pharmacological treatment episodes, with over half continuing to receive pharmacological treatment >90 days after first surgery. The proportion of patients who received pharmacological treatment >90 days after surgery was lower among those who underwent posterior fossa surgery than among those who underwent radiosurgery; nonetheless, the proportion was still substantial (Table 4).

Radiosurgery was most likely to be performed by neurosurgeons or at neurosurgical facilities (57.3% of procedures). Peripheral anesthetic injections were most likely to be performed by physicians or facilities specializing in anesthesiology (24.0%) or pain management/pain medicine (16.9%), while ablative procedures at the Gasserian ganglion were more likely to be administered in an acute care hospital (30.6%) or by neurologists/at neurology facilities (21.5%). Data were missing on specialty for most posterior fossa surgeries, although this surgery would be performed by a neurosurgeon.

Opioids

Overall, 65.6% of patients received opioids for any reason. A substantial proportion (42.9%) received opioids for TN, and 8.2% received them for ≥90 days (Table 2 and Table, Supplemental Digital Content 12, http://links.lww.com/CJP/A489). Even among those without pain comorbidities commonly treated with opioids, a high proportion had prescriptions for opioids (Table 2). Around one-fifth of patients who underwent posterior fossa surgery, and almost one-third of patients who underwent radiosurgery, continued to receive opioids >90 days after surgery (Table, Supplemental Digital Content 12, http://links.lww.com/CJP/A489).

Among patients who received TN-related opioids, 89.6% received ≥1 nonopioid pharmacological treatment episode, 62.7% received ≥2 episodes, and 44.7% received ≥3 episodes. The majority of patients who received opioids initiated opioid treatment while receiving nonopioid pharmacological treatment, while 10.8% received opioids before receiving a study drug. The median annual duration of opioid treatment ranged from 17 to 25 days across the 3 years (mean duration, 39 to 48 days; Table, Supplemental Digital Content 12, http://links.lww.com/CJP/A489). The mean number of opioid prescription refills was 2.7–2.8 (median 2.0).

DISCUSSION

This retrospective database claims analysis suggests that patients with TN in the United States frequently receive a variety of pharmacological treatments, surgeries, and injections to manage their condition, despite the limited evidence for most of these treatments. The most commonly used pharmacological treatment was carbamazepine, the only FDA-approved medication for TN; however, it was received by only half of patients, and high rates of other pharmacological treatments were also observed, particularly gabapentin. A substantial proportion of patients received multiple pharmacological treatment

episodes, indicating a high incidence of switching and/or add-on therapy. A relatively high proportion of patients underwent surgery within the first 3 years of diagnosis, including invasive posterior fossa surgery, and a high proportion continued to receive pharmacological treatment >90 days after first surgery (posterior fossa surgery, radiosurgery). Opioid use among patients with TN was prevalent, even among those without other pain conditions.

The severe pain experienced by patients with TN can lead to significant impairment of quality of life,[6] with outcomes for many remaining suboptimal, both because of a lack of efficacy and poor tolerability of available therapies. Few advances have been made in the treatment of TN in recent years, and at present there are no drugs that have been specifically developed for TN.[37] TN is unusual in being the only neuropathic pain that responds significantly to carbamazepine[10]; however, its poor tolerability profile and potential for drug interactions may have impacted its use.[11-15,17] This may explain in part our findings of an almost similarly high claim rate of gabapentin, for which there is limited evidence supporting efficacy, but which is viewed as having a better safety and tolerability profile than carbamazepine.[38] Further, our finding that carbamazepine and gabapentin were also the most frequently prescribed second- and third-line therapies suggests the lack of a well-established treatment pathway in TN, particularly in light of findings from other studies that report a relatively low use of gabapentin.[25] Surprisingly, lamotrigine use was very low despite a greater body of evidence to support its use in TN than either duloxetine or topiramate.[9,10]

Of the most commonly used pharmacological treatments, pregabalin and carbamazepine had the longest median durations as first-line pharmacological treatment. Pregabalin had the longest median duration as second-line pharmacological treatment, which could be due to its favorable twice-daily dosage scheme, along with fewer associated side effects than the older anticonvulsants. Overall, the median duration of first-line monotherapy was around 3 months, suggesting that this is the period over which patients typically

determine if a medication is working, although mean durations were longer, suggesting wide variations in the data and thus heterogeneity in both the disease course and treatment response.

We observed frequent changes in therapy and use of polypharmacy, with half of pharmacologically treated patients receiving ≥2 medications of interest, and around one-fifth receiving ≥3 medications of interest, perhaps owing to a lack of efficacy or tolerability of individual pharmacological treatments. The use of polypharmacy as a first-line treatment was observed despite a general consensus among clinicians to gradually titrate medications over time, and to initiate multiple drugs only once monotherapy has failed and prior to surgery.[25] Similar treatment patterns, including multiple drug use and only half of patients being prescribed carbamazepine, were noted in a prospective study by Zakrzewska et al among patients with TN referred to a specialist pain center in the United Kingdom.[6] In a large UK study by Hall et al, 58% of treated patients with TN were prescribed carbamazepine as an initial treatment, while substantially fewer were prescribed analgesics and amitriptyline (note that the study predated the introduction of gabapentin and pregabalin).[5] Further, more frequent treatment changes occurred when analgesics were used versus carbamazepine. In the current study, a notable proportion of patients with a diagnosis of TN did not receive pharmacological treatment, a finding in line with the Hall et al study, in which only 66% of patients with TN received pharmacological treatment. A smaller Dutch study noted that 97% of treated TN patients received a single drug as initial treatment versus 76% as subsequent treatment, while 3% were treated with 2 drugs as an initial treatment versus 23% as a subsequent treatment. They also found that primary care physicians were less likely to prescribe polypharmacy than neurologists for subsequent episodes. Adverse events were reported in 11% of first treatment episodes and 15% for subsequent treatment episodes.[24] Also of interest is a small study by Taylor et al showing the development of late resistance to

carbamazepine in 13% of patients who had a good initial response, which could further explain switching of therapy (although this might have been due to the natural history of the disorder or due to autoinduction).[39]

Overall, 12.3% of the study population underwent surgery during the 3 years following diagnosis, which is surprising so early in the disease course given the potential for remission. Radiosurgery was the most common surgical treatment among Medicare patients, while posterior fossa surgery was more common among commercial patients; this difference is almost certainly reflective of differences in the age of the populations, with radiosurgery being favored among the elderly as the less invasive procedure. Although anesthetic lidocaine may be beneficial in the management of acute episodes,[10] such injections generally have a short duration of effect, need repeating and, in the current study, were used by only a small percentage of all patients.

Over half of patients in the current study continued to receive pharmacological treatments >90 days after their first surgery, suggesting their pain may not be fully controlled by posterior fossa surgery or radiosurgery alone. Of further note is that an unexpectedly high proportion of patients (21.6%) did not receive any of the medications of interest before surgery, although the majority of these patients (81/98) received no pharmacological therapies of interest during the 3-year follow up period. Potential reasons for patients progressing to surgery before receiving pharmacological treatment may include a reluctance by physicians to prescribe medications such as carbamazepine, which may be poorly tolerated and/or a lack of knowledge of guideline recommended treatments. Physicians may have a greater familiarity with the use of gabapentin and pregabalin, both of which are used to treat a variety of neuropathic pain conditions, in contrast to carbamazepine, which is used exclusively for TN. Other reasons may include early referral to neurosurgeons due to uncertainty of the diagnosing physician around the management of TN and lack of

neurologists with an interest in headaches. It is also possible that some patients received treatments other than the 7 specified as of interest, or received treatment before documentation of their diagnosis or outside of the insurance network, such as those under the care of dental surgeons or orofacial pain experts who entered the system only once they required surgery.

The use of opioids was shown to be prevalent among patients with TN in this study, and has been previously noted in the UK study by Zakrzewska et al[6] and the Dutch study by Koopman et al.[24] This observation is of concern given the lack of evidence for the efficacy of opioids in TN and their risk of abuse.[29] That the use of opioids is high despite these issues suggests an absence of effective and tolerable alternatives, and that physicians may be prescribing opioids as a rescue therapy.

TN is an unusual chronic pain due to its episodic, variable and unpredictable nature, in terms of both the frequency and severity of attacks and its variable remission periods, particularly in the early years of the disease. The length of episodes can vary from 1 to 1462 days, and it is estimated that 65% are likely to experience a second episode within 5 years.[4] Initial remission could account for the fact that a quarter of patients in the current study with a TN diagnosis did not receive any of the studied treatments. It could also offer an explanation as to why the use of pharmacological treatment decreased in the 2 years after diagnosis. However, the decrease also could be reflective of patients proceeding to surgery, or switching to opioids or a nonstudied treatment. These potential reasons for stopping pharmacological therapy might also explain the reduction in the number of treatment episodes, although this could also be due to patients trialling multiple therapies in the first year, before continuing on one regimen that they found to be efficacious or tolerable. However, it is difficult to draw firm conclusions about the natural history of TN, as the relatively short duration of follow-up in the current study (3 years) does not capture the full

disease course of TN; further studies are needed with follow-up to examine trends over an extended period of time.

An important consideration for the interpretation of any dataset is the generalizability to the overall population with TN. The Truven Health MarketScan database provides a good basis for these analyses, given that it covers all regions of the United States and includes adults across all ages. However, we note that uninsured individuals and those on Medicaid were not captured, and that Medicare patients were likely underrepresented relative to commercial patients; Medicare patients included in MarketScan are covered by MediGap or Medicare managed care plans, which generally account for only a small proportion of Medicare enrollees.

Rates of comorbidities among patients with TN in this study appear generally consistent with the US population. For example, the proportion with diabetes was 12.7%, similar to a reported estimate of 11.9% in the general US population.[40] The prevalence of hypertension in the Medicare population (62.4%) was similar to a reported rate of 65.0% in the general US population >60 years of age, although the overall prevalence in this study was slightly higher (41.2% vs. 29.1%, respectively),[41] suggestive of a possible association between TN and hypertension that has been observed in other studies.[42] The overall prevalence was broadly comparable to a recent UK study of patients with TN, which reported that 37.7% of patients with TN had hypertension.[6] MS is the most frequently associated condition with TN; a meta-analysis by Foley et al reported that 4% of patients with MS are likely to have TN,[43] while in this series, 3% of patients had MS. This is compared with a prevalence rate of only 58/100,000 (0.058%) in the US population overall.[44] We noted that the proportion of women was slightly higher in this study than for the TN population reported in other literature 71.8% vs ~60%[6,8,45], respectively) and the authors' own practices, most

likely due to the fact that women are more likely to access care and typically live longer than men.

Limitations of this study that are inherent to claims analyses include that prescription fills do not necessarily reflect treatment usage, and that the analysis is reliant on the accurate documentation of diagnosis codes. Consistent with other claims analysis literature, we assumed that a claim was TN related if there was a medical claim with a TN diagnosis up to 30 days before or 7 days after the first prescription fill for each of the 7 medications of interest (or all prescriptions for opioids); however, prescriptions do not document the diagnosis code directly so we cannot be certain of the reasons for medication use. Dental claims were not captured in the database, which may be relevant given that many patients initially visit their dentist with TN pain and can receive both medications and irreversible treatments.[6] Additionally, we only evaluated specific medications and surgery/injections of interest; however, as these were selected based on expert clinical judgement, we are confident they are generally representative of the treatments utilized by patients with TN. The reasons for medication switches, discontinuation, and treatment outcomes cannot be fully explained with observational studies, and future studies should explore alternative designs to address these questions.

CONCLUSIONS

This large study provides evidence that patients with TN in the United States frequently receive a variety of pharmacological treatments, despite carbamazepine being the only approved medication for TN, and international guidelines recommending carbamazepine and oxcarbazepine as first-line treatments for pain control. We observed high rates of treatment switching and polypharmacy, suggestive of poor efficacy/tolerability of current available pharmacologic treatments. A notable proportion of patients undergo surgeries in the first 3 years following diagnosis, including patients who did not appear to trial

pharmacotherapy prior to surgery. Of concern, a substantial proportion of patients receive opioids, despite the lack of evidence for efficacy in TN and potential for abuse. Together, our findings indicate a high burden of illness associated with TN and its treatment, a need for education of healthcare professionals on the guideline recommended management of TN, and a remaining unmet need for therapies with robust efficacy and improved tolerability.

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Figures

FIGURE 1. Patient flow diagram.

Denominators for percentages are the n value for the preceding step. TN, trigeminal neuralgia.

FIGURE 2. Proportions using pharmacological treatment any time in 3 years, by individual medication, in the commercial (A) and Medicare (B) populations.

Total includes patients started on medications either as monotherapy or part of combination pharmacological therapy; the total therefore exceeds 100%. BAC, baclofen; CBZ, carbamazepine; DUL, duloxetine; GBP, gabapentin; OXC, oxcarbazepine; PGB, pregabalin; TOP, topiramate.

FIGURE 3. Number of surgeries/injections among treated patients in the (A) commercial and (B) Medicare populations.

Percentage within the bars represents the percentage breakdown by number of episodes. Denominator (n value) = total patients receiving each treatment type. Count of surgeries/injections per patient is based on claims for the same type of surgery/injection with unique service dates or admission dates (claims on the same service or admission date are grouped as 1 surgery/injection).

Supplemental Digital Content

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TABLE 1. Patient Demographics (Index) and Comorbidities (Pre Index)

	Total **N=3685**	**Commercial** **n=2425**	**Medicare** **n=1260**
Mean (SD) age (y)	59.0 (15.3)	49.8 (9.0)	76.8 (7.1)
Sex, n (%)			
Female	2646 (71.8)	1804 (74.4)	842 (66.8)
Male	1039 (28.2)	621 (25.6)	418 (33.2)
Geographical region, n (%)			
Northeast	776 (21.1)	539 (22.2)	237 (18.8)
North Central	996 (27.0)	538 (22.2)	458 (36.3)
South	1279 (34.7)	930 (38.4)	349 (27.7)
West	598 (16.2)	403 (16.6)	195 (15.5)
Unknown	36 (1.0)	15 (0.6)	21 (1.7)
Plan indicator, n (%)			
Comprehensive	761 (20.7)	115 (4.7)	646 (51.3)
PPO	1887 (51.2)	1431 (59.0)	456 (36.2)
HMO	420 (11.4)	326 (13.4)	94 (7.5)
Other*	617 (16.7)	553 (22.8)	64 (5.1)
Comorbidities, n (%)†			
Cerebrovascular disease	258 (7.0)	92 (3.8)	166 (13.2)
Hypertension	1520 (41.2)	734 (30.3)	786 (62.4)
Diabetes	468 (12.7)	232 (9.6)	236 (18.7)

Multiple sclerosis	112 (3.0)	90 (3.7)	22 (1.7)
Pain related‡			
Osteoarthritis	683 (18.5)	335 (13.8)	348 (27.6)
Lower back pain	667 (18.1)	423 (17.4)	244 (19.4)
Migraine	342 (9.3)	305 (12.6)	37 (2.9)
Fibromyalgia	332 (9.0)	259 (10.7)	73 (5.8)
Stroke-associated pain	297 (8.1)	107 (4.4)	190 (15.1)

*Other includes exclusive provider organization, point of service (POS), POS with capitation, consumer-directed health plan (CDHP), high-deductible health plan (HDHP); data by individual plan type is provided in Table, Supplemental Digital Content 4, http://links.lww.com/CJP/A481 . †Based on claims in the year before index date; diagnosis codes are listed in Table, Supplemental Digital Content 1. ‡Top 5 of 16 pain conditions (full list of 16: diabetic neuropathy, postherpetic neuropathy, stroke-associated pain, lumbar radiculopathy, cervical radiculopathy, multiple sclerosis–associated pain, fibromyalgia, osteoarthritis, lower back pain, migraine, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthropathy, cancer pain, irritable bowel syndrome, interstitial cystitis).

HMO, health maintenance organization; PPO, preferred provider organizer.

TABLE 2. Pharmacological and Nonpharmacological Treatment Use in the 3 Years Following Initial TN Diagnosis

	Total N=3685	**Commercial n=2425**	**Medicare n=1260**
Any treatment of interest, n (%)	2752 (74.7)	1789 (73.8)	963 (76.4)
Pharmacological treatment, n (%)*	2671 (72.5)	1750 (72.2)	921 (73.1)
Study medications received (excluding opioids), n (%)			
1	1333 (36.2)	852 (35.1)	481 (38.2)
2	835 (22.7)	534 (22.0)	301 (23.9)
3	339 (9.2)	234 (9.6)	105 (8.3)
≥4	164 (4.5)	130 (5.4)	34 (2.7)
Pharmacological treatment, ever added on or switched, n (%)*			
Ever added on or switched	1207 (32.8)	815 (33.6)	392 (31.1)
Ever added on	755 (20.5)	495 (20.4)	260 (20.6)
Ever switched	716 (19.4)	500 (20.6)	216 (17.1)
Posterior fossa surgery, n (%)	222 (6.0)	168 (6.9)	54 (4.3)
Radiosurgery, n (%)	269 (7.3)	127 (5.2)	142 (11.3)
Peripheral anesthetic injections, n (%)	207 (5.6)	161 (6.6)	46 (3.7)
Gasserian ganglion procedures, n (%)	92 (2.5)	61 (2.5)	31 (2.5)
Received opioids for any reason, n (%)	2418 (65.6)	1635 (67.4)	783 (62.1)
Received opioids for TN, n (%)†	1582 (42.9)	1076 (44.4)	506 (40.2)

Opioid use in patients *without* pain comorbidities‡	733 (39.3) n=1864	523 (40.8) n=1281	210 (36.0) n=583
Opioid use in patients *with* pain comorbidities‡	849 (46.6) n=1821	553 (48.3) n=1144	296 (43.7) n=677

*Medications of interest: carbamazepine, oxcarbazepine, pregabalin, gabapentin, baclofen, duloxetine, topiramate. †Medical claim within −30 to +7 days of an opioid prescription fill. ‡Pain comorbidities: diabetic neuropathy, postherpetic neuropathy, stroke-associated pain, lumbar radiculopathy, cervical radiculopathy, multiple sclerosis–associated pain, fibromyalgia, osteoarthritis, lower back pain, migraine, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthropathy, cancer pain, irritable bowel syndrome, interstitial cystitis.

TN, trigeminal neuralgia.

TABLE 3. Proportion and Duration of First-line Monotherapy by Medication (Among Patients Receiving Monotherapy as First-Line Treatment)

Medication		Total N=2324	Commercial n=1520	Medicare n=804
Carbamazepine, first-line monotherapy, n (%)		899 (38.7)	584 (38.4)	315 (39.2)
Duration (days)	Median (IQR)	90 (30–370)	58 (30–245)	145 (39–644)
	Mean (SD)	271 (361)	223 (329)	359 (401)
Gabapentin, first-line monotherapy, n (%)		740 (31.8)	466 (30.7)	274 (34.1)
Duration (days)	Median (IQR)	86 (30–286)	69 (30–265)	112 (30–366)
	Mean (SD)	246 (342)	224 (324)	285 (367)
Oxcarbazepine, first-line monotherapy, n (%)		271 (11.7)	165 (10.9)	106 (13.2)
Duration (days)	Median (IQR)	80 (30–387)	65 (30–384)	124 (30–463)
	Mean (SD)	270 (354)	252 (346)	300 (365)
Pregabalin, first-line monotherapy, n (%)		204 (8.8)	137 (9.0)	67 (8.3)
Duration (days)	Median (IQR)	90 (30–341)	59 (28–223)	149 (32–558)
	Mean (SD)	266 (370)	232 (359)	335 (384)
Topiramate, first-line monotherapy, n (%)		106 (4.6)	90 (5.9)	16 (2.0)
Duration (days)	Median (IQR)	31 (23–193)	38 (23–260)	30 (21–71)

(days)	Mean (SD)	233 (367)	250 (379)	137 (283)
Duloxetine, first-line monotherapy, n (%)		67 (2.9)	53 (3.5)	14 (1.7)
Duration	Median (IQR)	99 (27–368)	99 (28–363)	108 (21–368)
(days)	Mean (SD)	308 (394)	304 (386)	320 (435)
Baclofen, first-line monotherapy, n (%)		37 (1.6)	25 (1.6)	12 (1.5)
Duration	Median (IQR)	30 (13–178)	30 (20–256)	20 (4–30)
(days)	Mean (SD)	100 (146)	130 (165)	38 (61)

IQR, interquartile range.

TABLE 4. Among Those With Surgery, Pharmacological Treatment Episodes Before and After First Surgery

	Total	**Commercial**	**Medicare**
	N=454[†]	**n=271**	**n=183**
Pharmacological treatment episodes before first surgery, n (%)			
0	98 (21.6)	48 (17.7)	50 (27.3)
1	123 (27.1)	64 (23.6)	59 (32.2)
≥2	233 (51.3)	159 (58.7)	74 (40.4)
Pharmacological treatment episodes after first surgery, n (%)			
0	116 (25.6)	62 (22.9)	54 (29.5)
1	134 (29.5)	80 (29.5)	54 (29.5)
≥2	204 (44.9)	129 (47.6)	75 (41.0)
Pharmacological treatment >90 days after first surgery, n (%)	237 (52.2)	148 (54.6)	89 (48.6)
Posterior fossa surgery*	85 (42.3)	71 (45.2)	14 (31.8)
	n=201	n=157	n=44
Radiosurgery*	152 (60.1)	77 (67.5)	75 (54.0)
	n=253	n=114	n=139

*Denominator (n value) = total number with surgery type. [†]Of the overall population, 81 of 454 patients did not receive any pharmacological treatment during the 3-year follow up period.

Supplemental Digital Content 1. Comorbidity Diagnosis Codes

Comorbidity	**Diagnosis code(s)**
Depression	2962, 2963, 311, F33, F32
Anxiety	3000, 3001, 3002, 3003, 3004, 3005, 3006, 3007, 3008, F423, F429, F422, F428, F341, F488, F481, F4522, F4521
Insomnia	30742, 30741, 3270, 78051, 78052, F5102, F5109, F5103, F5101, F5109, G4730, G4700
Stroke	430, 431, 432, 433, 434, 436
Hypertension	401, 402, 403, 404, 405
Multiple sclerosis	340
Diabetes	250
Pain conditions	
Diabetic neuropathy	2506, 3572
Postherpetic neuropathy	05310, 05311, 05312, 05313, 05314, 05319
Stroke-associated pain	430, 431, 432, 433, 434, 436, 437, 3380
Lumbar radiculopathy	7244
Cervical radiculopathy	7234
Multiple sclerosis–associated pain	340, 3380
Fibromyalgia	7291
Osteoarthritis	7150, 7151, 7152, 7158, 7159, 7210, 7211, 7212, 7213, 72141, 72142
Lower back pain	72283, 72402, 7242, 7245, 7248

Migraine	3460, 3461, 3462, 3468, 3469
Rheumatoid arthritis	7140, 7141, 7142, 71430, 71431, 71432, 71433, 7144, 71481
Ankylosing spondylitis	7200, 7201, 7202, 72081, 72089
Psoriatic arthropathy	696
Cancer pain	3383
Irritable bowel syndrome	5641
Interstitial cystitis	5951

Supplemental Digital Content 2. Definitions Used to Define Pharmacological Treatment Episodes

Add-on therapy	A claim for a new medication, filled with ≥30-day overlap in prescription coverage relative to the prior treatment episode (based on days' supply)
Treatment switch	A claim for a new medication, filled with <30-day overlap in prescription coverage relative to the prior treatment episode
Discontinuation	A gap of ≥90 days between fills (from the last day of supply to the next fill date)
Treatment episode	Any unique pharmacological treatment regimen (monotherapy or combination), with the end of each episode defined by a change in regimen (add-on, switch, or discontinuation)
Duration of treatment episode	Based on the time from the first day of supply to last day of supply (for discontinuations) or the fill date of a new treatment episode (for treatment add-on or switch)

Supplemental Digital Content 3. Surgery/Injection Treatment Codes

Code type	Code	Procedure
Posterior fossa surgery		
CPT	61450	Craniectomy, subtemporal, for section, compression, or decompression of sensory root of Gasserian ganglion
CPT	61458	Craniectomy, suboccipital, for exploration or decompression of cranial nerves
CPT	61460	Craniectomy, suboccipital, for section of ≥1 cranial nerves
ICD	0402	04.02 Division of trigeminal nerve
ICD	0405	Gasserian ganglionectomy
ICD	0441	04.41 Decompression of trigeminal nerve root
ICD	0124	01.24 Other craniotomy
ICD	0139	01.39 Other incision of brain
ICD	0159	01.59 Other excision or destruction of lesion or tissue of brain
ICD	0299	02.99 Other operations on skull, brain, and cerebral meninges
ICD	0404	04.04 Other incision of cranial and peripheral nerves
ICD	0407	04.07 Other excision or avulsion of cranial and peripheral nerves
ICD	0419	04.19 Other diagnostic procedures on cranial and peripheral nerves and ganglia
ICD	0449	04.49 Other peripheral nerve or ganglion decompression

		or lysis of adhesions
ICD	046	04.6 Transposition of cranial and peripheral nerves
ICD	0499	04.99 Other operations on cranial and peripheral nerves
ICD	0529	05.29 Other sympathectomy and ganglionectomy
Radiosurgery		
CPT	61796	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator), 1 simple cranial lesion
CPT	61797	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator), each additional cranial lesion, simple (list separately in addition to code for primary procedure)
CPT	61798	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator), 1 complex cranial lesion
CPT	61799	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator), each additional cranial lesion, complex (list separately in addition to code for primary procedure)
CPT	61790	Creation of lesion by stereotactic method, percutaneous, by neurolytic agent (eg, alcohol, thermal, electrical, radiofrequency), Gasserian ganglion
CPT	61791	Creation of lesion by stereotactic method, percutaneous, by neurolytic agent (eg, alcohol, thermal, electrical, radiofrequency), trigeminal medullary tract
CPT	77371	Radiation treatment delivery, stereotactic radiosurgery, complete course of treatment of cranial lesion(s) consisting of 1 session, multisource cobalt 60 based
HCPC	G0173	Stereo radiosurgery, complete

HCPC	G0251	Collimator changes and custom plugging, fractionated treatment, all lesions, per session, maximum 5 sessions per course of treatment
HCPC	G0339	Complete course of therapy in 1 session or first session of fractionated treatment
HCPC	G0340	Delivery including collimator changes and custom plugging, fractionated treatment, all lesions, per session, second through fifth sessions, maximum
ICD	9224	92.24 Teleradiotherapy using photons
ICD	9229	92.29 Other radiotherapeutic procedure
ICD	9230	92.30 Stereotactic radiosurgery, not otherwise specified
ICD	9231	92.31 Single-source photon radiosurgery
ICD	9232	92.32 Multisource photon radiosurgery
ICD	9233	92.33 Particulate radiosurgery

Peripheral anesthetic injection

CPT	64400	Destruction by neurolytic agent, trigeminal nerve; supraorbital, infraorbital, mental, or inferior alveolar branch
ICD	0480	04.80 Peripheral nerve injection, not otherwise specified
ICD	0481	04.81 Injection of anesthetic into peripheral nerve for analgesia
ICD	0489	04.89 Injection of other agent, except neurolytic
ICD	0531	05.31 Injection of anesthetic into sympathetic nerve for analgesia
ICD	0539	05.39 Other injection into sympathetic nerve or ganglion

ICD	8398	83.98 Injection of locally acting therapeutic
ICD	9929	99.29 Injection or infusion of other therapeutic or prophylactic substance
CPT	64612	Chemodenervation of muscle(s); muscle(s) innervated by facial nerve, unilateral (eg, for blepharospasm, hemifacial spasm)
Ablative procedures at the Gasserian ganglion		
CPT	64600	Destruction by neurolytic agent, trigeminal nerve, supraorbital, infraorbital, mental, or inferior alveolar branch
CPT	64605	Destruction by neurolytic agent, trigeminal nerve, second and third division branches at foramen ovale
CPT	64610	Destruction by neurolytic agent, trigeminal nerve, second and third division branches at foramen ovale under radiologic monitoring
ICD	0532	05.32 Injection of neurolytic agent into sympathetic nerve

CPT, Current Procedural Terminology; HCPC, Healthcare Common Procedure Code; ICD, International Classification of Diseases.

Supplemental Digital Content 4. Proportion of Patients by Health Care Plan Type

Plan indicator, n (%)	**Total N=3685**	**Commercial n=2425**	**Medicare n=1260**
Comprehensive	761 (20.7)	115 (4.7)	646 (51.3)
PPO	1887 (51.2)	1431 (59.0)	456 (36.2)
HMO	420 (11.4)	326 (13.4)	94 (7.5)
EPO	30 (0.8)	29 (1.2)	1 (0.1)
POS	300 (8.1)	257 (10.6)	43 (3.4)
POS with capitation	14 (0.4)	14 (0.6)	–
CDHP	149 (4.0)	147 (6.1)	2 (0.2)
HDHP	71 (1.9)	70 (2.9)	1 (0.1)
Missing	53 (1.4)	36 (1.5)	17 (1.4)

CDHP, consumer-directed health plan; EPO, exclusive provider organization; HDHP, high-deductible health plan; HMO, health maintenance organization; PPO, preferred provider organization; POS, point of service.

Supplemental Digital Content 5. Treatment Switch Patterns Among Patients Treated With Pharmacological Treatment or Surgeries

Treatment type, n (%)	First treatment n=2752	Second treatment n=1795	Thrid treatment n=1223
Monotherapy*	2324 (84.4)	1131 (63.0)	795 (65.0)
Polypharmacy*	330 (12.0)	541 (30.1)	332 (27.1)
Surgery (posterior fossa surgery or radiosurgery only)	98 (3.6)	123 (6.9)	96 (7.8)

*Medications of interest: carbamazepine, oxcarbazepine, pregabalin, gabapentin, baclofen, duloxetine, topiramate

Supplemental Digital Content 6. Number of Pharmacological Treatment Episodes Among Patients Treated With Pharmacological Treatment Over the 3-Year Study Period

Treatment episodes, n (%)	**Total N=2671**	**Commercial n=1750**	**Medicare n=921**
1	948 (35.5)	618 (35.3)	330 (35.8)
2	613 (23.0)	398 (22.7)	215 (23.3)
3	415 (15.5)	275 (15.7)	140 (15.2)
4	231 (8.7)	145 (8.3)	86 (9.3)
5	172 (6.4)	112 (6.4)	60 (6.5)
6 to 10	268 (10.0)	182 (10.4)	86 (9.3)
≥11	24 (0.9)	20 (1.1)	4 (0.4)

Supplemental Digital Content 7. Pharmacological Treatment Episodes by Year of Follow-up Among the Overall Population

Treatment episodes, n (%)	**Total N=3685**	**Commercial n=2425**	**Medicare n=1260**
Year 1			
0	1099 (29.8)	734 (30.3)	365 (29.0)
1	1383 (37.5)	878 (36.2)	505 (40.1)
2	624 (16.9)	424 (17.5)	200 (15.9)
≥3	579 (15.7)	389 (16.0)	190 (15.1)
Year 2			
0	1900 (51.6)	1323 (54.6)	577 (45.8)
1	1235 (33.5)	740 (30.5)	495 (39.3)
2	319 (8.7)	204 (8.4)	115 (9.1)
≥3	231 (6.3)	158 (6.5)	73 (5.8)
Year 3			
0	2049 (55.6)	1412 (58.2)	637 (50.6)
1	1133 (30.8)	690 (28.5)	443 (35.2)
2	274 (7.4)	174 (7.2)	100 (7.9)
≥3	229 (6.2)	149 (6.1)	80 (6.3)

Supplemental Digital Content 8. Proportion and Duration of Second-Line Monotherapy by Medication

Medication		Total N=1130	Commercial n=750	Medicare n=380
Carbamazepine, second-line monotherapy, n (%)		338 (29.9)	211 (28.1)	127 (33.4)
Duration (days)	Median (IQR)	90 (30–269)	80 (30–210)	145 (35–371)
	Mean (SD)	204 (252)	174 (230)	252 (279)
Gabapentin, second-line monotherapy, n (%)		364 (32.2)	231 (30.8)	133 (35)
Duration (days)	Median (IQR)	90 (30–253)	64 (30–198)	134 (30–366)
	Mean (SD)	199 (255)	172 (241)	245 (272)
Oxcarbazepine, second-line monotherapy, n (%)		165 (14.6)	110 (14.7)	55 (14.5)
Duration (days)	Median (IQR)	90 (30–370)	85 (30–342)	103 (36–547)
	Mean (SD)	248 (305)	231 (297)	282 (319)
Pregabalin, second-line monotherapy, n (%)		138 (12.2)	96 (12.8)	42 (11.1)
Duration (days)	Median (IQR)	133 (30–344)	121 (30–339)	181 (79–388)
	Mean (SD)	256 (295)	239 (290)	294 (307)
Topiramate, second-line monotherapy, n (%)		47 (4.2)	43 (5.7)	4 (1.1)
Duration (days)	Median (IQR)	61 (30–128)	65 (30–130)	30 (30–38)

(days)	Mean (SD)	121 (186)	129 (192)	34 (8)
Duloxetine, second-line monotherapy, n (%)		41 (3.6)	32 (4.3)	9 (2.4)
Duration	Median (IQR)	138 (47–403)	137 (39–369)	322 (104–540)
(days)	Mean (SD)	300 (339)	286 (343)	348 (340)
Baclofen, second-line monotherapy, n (%)		37 (3.3)	27 (3.6)	10 (2.6)
Duration	Median (IQR)	41 (30–144)	42 (25–153)	32 (30–90)
(days)	Mean (SD)	142 (238)	172 (272)	59 (50)

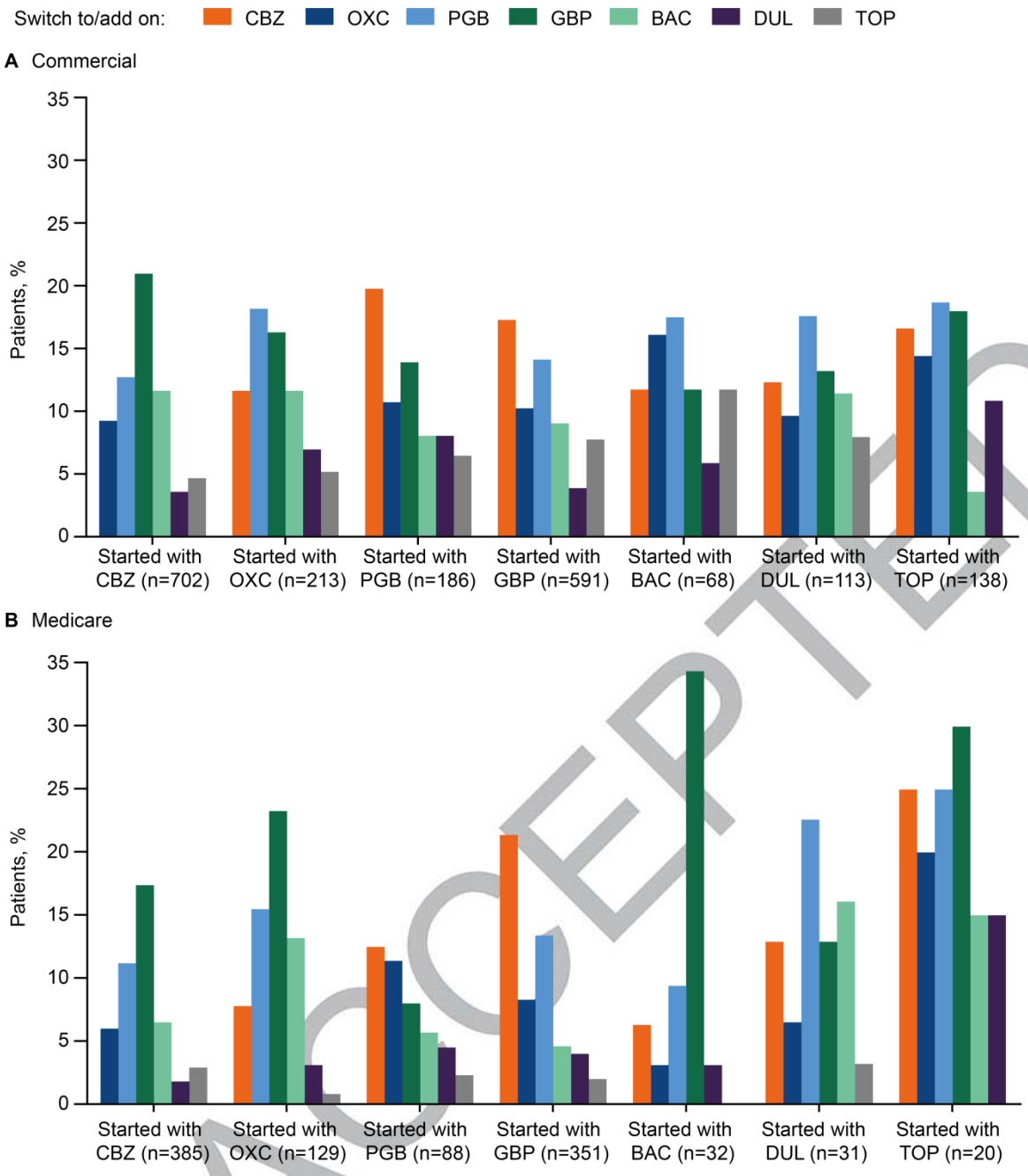
IQR, interquartile range.

Supplemental Digital Content 9. Proportion and Duration of Third-line Monotherapy by Medication

Medication		Total N=796	Commercial n=508	Medicare n=288
Carbamazepine, third-line monotherapy, n (%)		247 (31.0)	155 (30.5)	92 (31.9)
Duration (days)	Median (IQR)	33 (30–107)	30 (30–104)	39 (30–124)
	Mean (SD)	108 (172)	91 (134)	135 (219)
Gabapentin, third-line monotherapy, n (%)		238 (29.9)	143 (28.2)	95 (33.0)
Duration (days)	Median (IQR)	46 (30–109)	45 (30–109)	47 (30–110)
	Mean (SD)	96 (131)	92 (118)	103 (149)
Oxcarbazepine, third-line monotherapy, n (%)		98 (12.3)	60 (11.8)	38 (13.2)
Duration (days)	Median (IQR)	36 (30–90)	30 (23–90)	51 (30–90)
	Mean (SD)	111 (204)	107 (212)	117 (193)
Pregabalin, third-line monotherapy, n (%)		97 (12.2)	61 (12.0)	36 (12.5)
Duration (days)	Median (IQR)	34 (30–158)	34 (30–140)	37 (8–239)
	Mean (SD)	122 (168)	105 (131)	152 (216)
Topiramate, third-line monotherapy, n (%)		50 (6.3)	44 (8.7)	6 (2.1)
Duration (days)	Median (IQR)	30 (28–75)	30 (22–75)	41 (30–58)

(days)	Mean (SD)	68 (86)	71 (91)	49 (27)
Duloxetine, third-line monotherapy, n (%)		33 (4.2)	20 (3.9)	13 (4.5)
Duration	Median (IQR)	86 (30–187)	45 (30–155)	159 (82–337)
(days)	Mean (SD)	156 (174)	114 (134)	222 (211)
Baclofen, third-line monotherapy, n (%)		33 (4.2)	25 (4.9)	8 (2.8)
Duration	Median (IQR)	47 (28–156)	75 (28–156)	39 (19–143)
(days)	Mean (SD)	140 (193)	156 (211)	93 (116)

IQR, interquartile range.



Supplemental Digital Content 10. Pharmacological treatment switch/add on patterns, by medication, in the commercial (A) and Medicare (B) populations.

BAC, baclofen; CBZ, carbamazepine; DUL, duloxetine; GBP, gabapentin; OXC, oxcarbazepine; PGB, pregabalin; TOP, topiramate.

Supplemental Digital Content 11. Duration in Days, From First TN Diagnosis to First Surgery Among Patients Who Underwent Surgery, and From Initial Pharmacological Treatment to First Surgery Among Patients Who Received Pharmacological Treatment Before Surgery

	Total	**Commercial**	**Medicare**
	N=454	**n=271**	**n=183**
Days from TN diagnosis to first surgery			
Median (IQR)	226 (76–514)	300 (96–570)	133 (55–419)
Mean (SD)	329 (302)	364 (300)	277 (298)
Days from starting pharmacological treatment to first surgery*	n=356	n=223	n=133
Median (IQR)	224 (81–488)	292 (95–539)	132 (63–399)
Mean (SD)	322 (292)	355 (294)	266 (281)

*Among patients who received pharmacological treatment before surgery (17 patients received surgery before pharmacological treatment; 81 patients did not receive pharmacological treatment and were excluded from this analysis).

IQR, interquartile range; TN, trigeminal neuralgia.

Supplemental Digital Content 12. Overall and TN-Related Opioid Use*

	Total	**Commercial**	**Medicare**
	N=3685	**n=2425**	**n=1260**
Opioids (any use), n (%)	2418 (65.6)	1635 (67.4)	783 (62.1)
≥90 days of opioid use over 3 years, n (%)	693 (18.8)	470 (19.4)	223 (17.7)
TN-related opioid use, n (%)*	1582 (42.9)	1076 (44.4)	506 (40.2)
≥90 days of opioid use over 3 years, n (%)	303 (8.2)	223 (9.2)	80 (6.3)
TN-related opioid use*	**n=1582**	**n=1076**	**n=506**
Nonopioid pharmacological treatment episodes, n (%)			
0	165 (10.4)	112 (10.4)	53 (10.5)
1	425 (26.9)	290 (27.0)	135 (26.7)
2	285 (18.0)	181 (16.8)	104 (20.6)
≥3	707 (44.7)	493 (45.8)	214 (42.3)
Opioid use initiation relative to pharmacological treatment episodes, n (%)			
Did not receive pharmacological treatment	165 (10.4)	112 (10.4)	53 (10.5)
Initiated opioids before first pharmacological treatment	171 (10.8)	129 (12.0)	42 (8.3)
Initiated opioids after last pharmacological treatment	68 (4.3)	43 (4.0)	25 (4.9)
Initiated opioids concurrently with pharmacological treatment	1178 (74.5)	792 (73.6)	386 (76.3)

		Denominators vary		
Opioid use in patients who *did* receive surgery within 3 years, n (%)		310 (68.3) n=454	206 (76.0) n=271	104 (56.8) n=183
Opioid use in patients who *did not* receive surgery within 3 years, n (%)		1272 (39.4) n=3231	870 (40.4) n=2154	402 (37.3) n=1n,077
Opioid use >90 days after posterior fossa surgery, n (%)		44 (21.9) n=201	35 (22.3) n=157	9 (20.5) n=44)
Opioid use >90 days after radiosurgery, n (%)		76 (30.0) n=253	40 (35.1) n=114	36 (25.9) n=139
Opioid use in patients *without* OA, RA, and lower back pain		1039 (40.7) n=2553	757 (42.6) n=1779	282 (36.4) n=774
Opioid use in patients *with* OA, RA, and lower back pain		543 (48.0) n=1132	319 (49.4) n=646	224 (46.1) n=486
Duration of opioid treatment by year (days)				
	Median	17	17	19
Year 1	Mean (SD)	39 (51) n=1309	40 (54) n=911	35 (42) n=398
	Median	22	24	20
Year 2	Mean (SD)	44 (56) n=517	50 (63) n=342	33 (39) n=175
	Median	25	30	20
Year 3	Mean (SD)	48 (62) n=451	53 (68) n=310	37 (47) n=141

*Opioids with a TN claim −30 to +7 days.

OA, osteoarthritis; RA, rheumatoid arthritis; TN, trigeminal neuralgia.

Figure 1

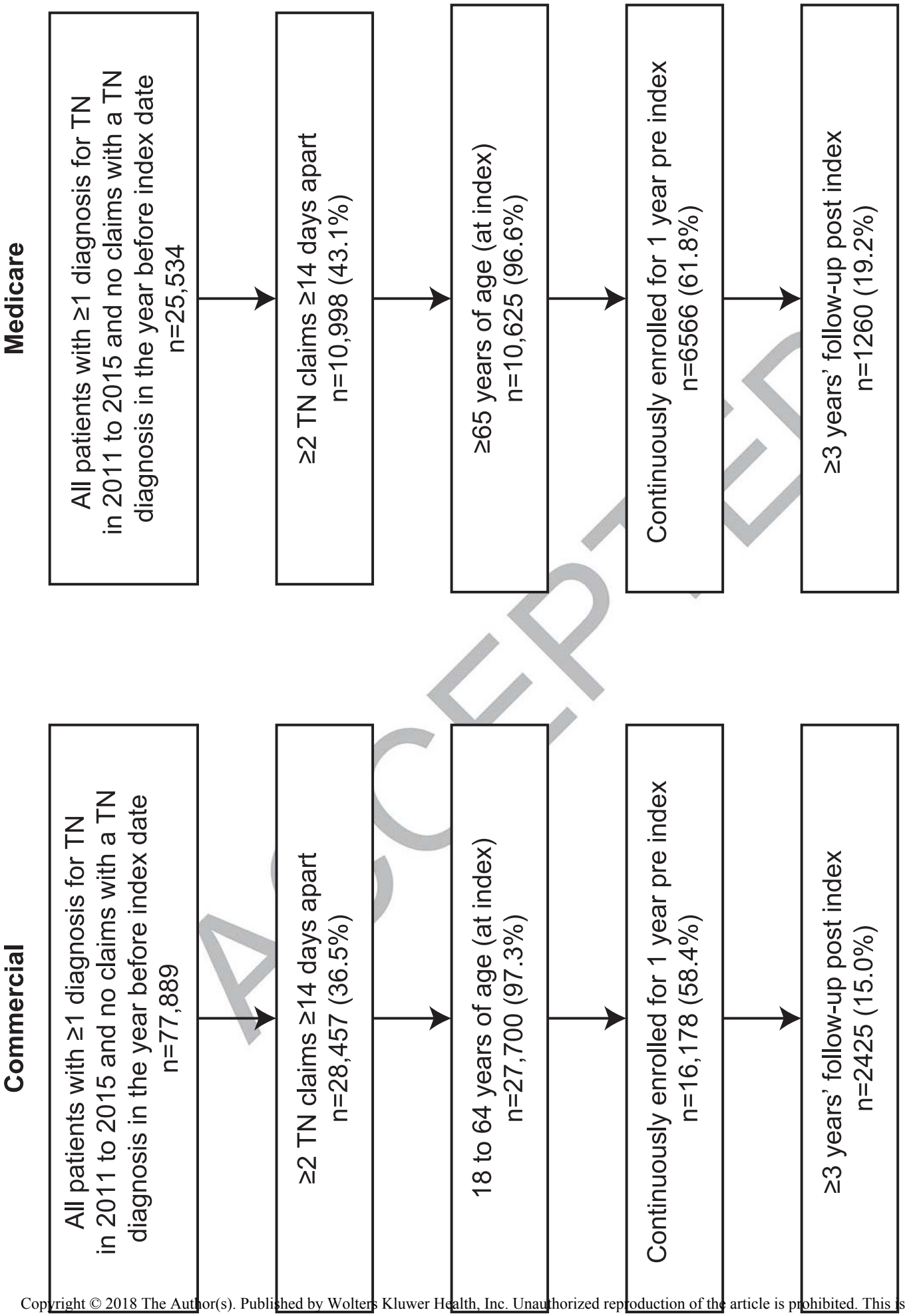


Figure 2

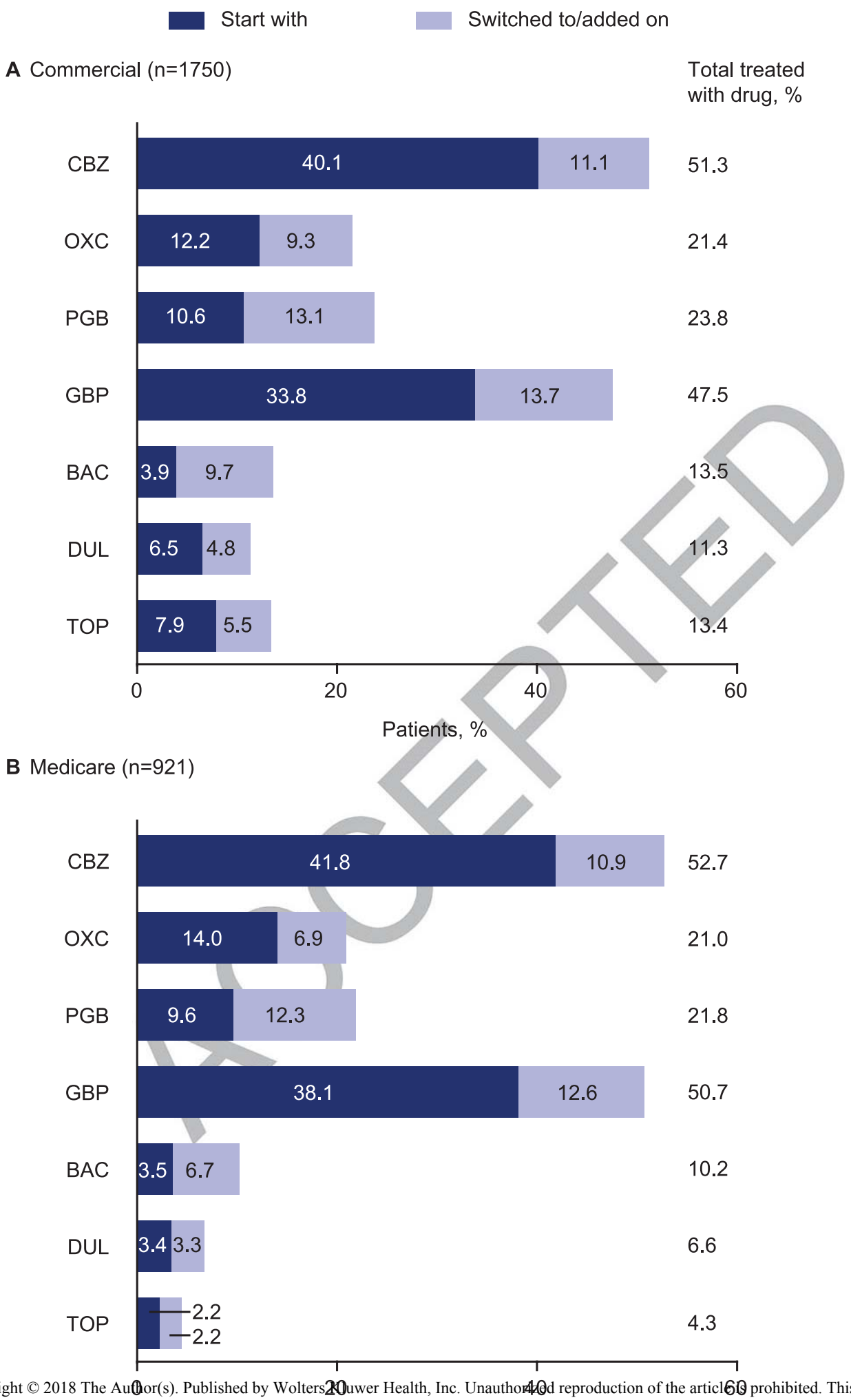


Figure 3