Survey

Comparative Descriptive Analysis of Physician Versus Patient-Directed Gabapentin Usage In Chronic Pain – A Preliminary Report

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Background: Gabapentin is one of the most common medications employed in Pain Medicine, specifically targeting the management of neuropathic pain. We are most familiar with the incremental dosing strategy where a ceiling dose is eventually attained guided by efficacy and patient tolerance, after which a fixed dosing regimen is prescribed. We propose that autonomous short-term dose variations per patient could have rapid clinically significant effects in the management of chronic pain.

Objectives: This study examines the frequency at which patients take gabapentin on a fixed vs variable schedule and how the pattern of gabapentin use correlates with efficacy, side effects, and patient satisfaction.

Study Design: Single institution, cross-sectional observational survey study with data collection performed over 2 phases as a pilot for proof of concept.

Setting: Remote contact via telephone with researchers calling from a quiet, private location within the hospital complex conducive for confidential conversation.

Methods: Patients recently prescribed gabapentin were queried on the patterns of use and self-perceived efficacy, satisfaction, and side effects in accordance to a standardized oral script. Patients selected met the criteria of being new patients freshly prescribed gabapentin who have been consistently on the medication for at least a month, while having chronic pain symptoms for over 3 months. Responses were collected in the form of a 5-point Likert scale. Statistical analyses were performed using GraphPad Prism.

Results: Of the 222 patients, 92 patients agreed to participate in the survey for a response rate of 41.4. Of these, 51% had terminated the medication for various reasons. Of the patients still taking gabapentin, 73% were on a fixed schedule, while 27% were on a variable dosing schedule. Variable dosing cohort reported better efficacy ($P = 0.027$) and satisfaction ($P = 0.036$), while the side-effect profile between the 2 groups was similar.

Limitations: The study is limited by its nature of being a pilot, single-institution study performed on a relatively small sample size. None of the patients we surveyed had been given the autonomy to adjust gabapentin doses by their providers and this could significantly reduce the proportion of patients who would be encouraged to run a variable dosing regimen.

Conclusions: This pilot study suggests that a significant portion of patients choose to administer variable doses of gabapentin and associate this with better efficacy and satisfaction. A larger study is needed to confirm this supposition. Based upon this pilot study, the variable dosing option may be an option for improved therapeutic efficacy or as an alternative to those whose lifestyles do not allow for fixed dosing regimens. Discussion of the risks of gabapentin, including respiratory depression, and clear dosage parameters of use, would need to be outlined when considering a variable dose regimen.

Key words: gabapentin, chronic pain, physician directed, patient directed

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Gabapentin is one of the most common medications employed in Pain Medicine, specifically targeting the management of neuropathic pain. This is widely practiced following emerging evidence supporting its efficacy in the management of postherpetic neuralgia and diabetic neuropathy, subsequently extending into other etiologies of neuropathic pain, including chronic back pain and cancer pain (1). In the context of a 7% to 10% prevalence of neuropathic pain in the general population (2), having gabapentin as an off-label substitute to more traditional agents, such as carbamazepine and tricyclic antidepressants, has been crucial in enhancing the pain arsenal.

Classed as an amino acid with structural similarity to the endogenous neurotransmitter GABA (3,4), it is thought that gabapentin interacts with the alpha-2-delta subunit of voltage-gated calcium channels in the central and peripheral nervous system, impeding calcium influx, and thereby reducing the reciprocal release of the excitatory neurotransmitters, such as glutamate, noradrenaline, and substance P (3).

The most frequently used dosing strategy consists of a starting dose of 300 mg with progressive increments by 300 mg daily to a ceiling of 3,600 mg guided by symptom alleviation or compromise in patients' tolerance (1). Sedation, confusion, and dizziness are some of the side effects most often quoted for termination when up-titrating the agent. Once an appropriate dose has been attained from the initial up-titration, it is recommended that patient take medication strictly on schedule and not as needed. This is based on studies (5,6) for both postherpetic neuralgia and diabetic neuropathy where gabapentin was administered on a fixed schedule, albeit with a dosing regimen of steady up-titration over the same period. On the molecular level, gabapentin exhibits high affinity for voltage-gated calcium channels, while inhibiting voltage-gated sodium channels. It also alters synthesis and release of GABA, serotonin, as well as monoamine neurotransmitters, the extent of contribution of each of these mechanisms to pain control is not known (5). Taking into consideration the escalating doses of gabapentin employed in these studies, it is not clear how much of the increased benefits over time could be attributed to the short-term up-titration in dose vs the long-term serum accumulation resulting in altered neurochemistry. Given that gabapentin has a short half-life and side effects that are in keeping with its duration of effect, it is possible that some analgesic effects of the drug are also immediate. Therefore, we hypothesize that gabapentin could be considered an as-needed medication amenable to patients' self-adjustment when used for relief of chronic pain. Furthermore, anecdotally in clinical practice, patients do use gabapentin at varying doses for a variety of reasons, including the desire to minimize medication intake and reduce side effects, while still reaping therapeutic benefits from a degree of continual use. This frequency of patient-initiated variable use is unknown. Through this study, we seek to establish therapeutic efficacy, side-effect profiles, and the level of satisfaction associated with patient-initiated variable gabapentin dosing strategy compared to the traditional clinician-directed fixed dosing regimen.

Methods

Data Collection

We conducted a single institution cross-sectional survey study with data collection performed over 2 phases as a pilot study for proof of concept. Patient lists of 4 different Pain Medicine attendings at The Arnold-Warfield Pain Center at Beth Israel Deaconess Medical Center were acquired through the online medical record (OMR) for the years 2020 and 2021. Inclusion criteria for patient selection consisted of (1) new patient visit within the 2020 to 2021 window; (2) new prescription of gabapentin within the 2020 to 2021 window; (3) consistent gabapentin use following prescription for at least one month; and (4) defined diagnosis of chronic pain lasting > 3 months. Exclusion criteria included patients who were unable to provide consent or communicate effectively and coherently through the telephone. Patient data collected included medical record number, age, gender, contact number, date of first patient visit, date of first gabapentin prescription, and chronic pain etiology.

Phase 2 of data collection comprised contacting the patients meeting inclusion criteria and conducting the telephone survey. A verbal consent was first obtained and formally documented (Appendix A) and subsequently the survey questionnaire was completed in the steps stipulated on the form (Appendix B). Four independent researchers conducted the telephone conversation in a completely private and quiet location within the hospital complex, each contacting a similar number of patients to minimize bias. Novel data collected on the questionnaire included the pattern of gabapentin consumption (fixed vs variable dosing), treatment efficacy, adverse effects experienced, level

of satisfaction on treatment, and if no longer on treatment - the reason(s) for stopping and its side effect(s). Each data point is scored out of 5 on the Likert scale, ranging from "Not at all effective" to "Extremely effective."

Study methodology was thoroughly evaluated by the hospital institutional review board office and was deemed to meet exemption criteria. All data were retrieved, collected, and stored in hospital computers on its network-shared drive behind a firewall.

Statistical Analysis

All statistical analyses in this article were performed using GraphPad Prism (GraphPad Software, Inc; San Diego, CA). For the calculation of continuous variables, the unpaired Student t test was used. For categorical variables, the Fisher's exact test was used. $P < 0.05$ was defined as the point of statistical significance. This is a pilot study and no previous data to calculate sample size was available. We estimated a survey sample of > 90 patients, which would be able to provide a reasonable approximation of patient use variability and outcomes that would also be clinically useful to gauge the extent of the variable gabapentin dosing practice.

Results

In the months of January and February 2022, a total of 222 patients were identified by 4 independent researchers using the above criteria, with approximately equal numbers of patients coming from each attending. We acquired responses from 92 patients, achieving a response rate of 41.4% after a minimum of 2 attempts at reaching each patient via each contact number listed on the OMR. Forty-five patients (48.9%) were actively taking gabapentin, while the remaining 47 (51.1%) had terminated their gabapentin regimens at the time of contact. The percentage of patients < 60 years of age was 54.3%, and 45.7% were ≥ 60 years of age, with the youngest being 21 and oldest 92. Thirty-eight percent of these patients were men, and 62% were women. Common locations of pain were situated in the torso, head and neck, and the extremities. Of the patients continuing gabapentin, 73% (33 out of 45) were on a fixed dosing regimen, while 27% (12 out of 45) were on a variable regimen. Basic demographics and characteristics of the surveyed population were summarized in Table 1.

For patients who continued taking gabapentin, there was no significant difference in the mean age between those who remained on fixed gabapentin dosing (59.2, 95% CI 53.6-64.9 years) vs those who had varied their dosing (65.1, 95% CI 55.8-74.4 years, $P = 0.27$). The ratio of men to women was 1:1.1 in the fixed dosing and 5:1 ($P = 0.086$) in the variable dosing group (Table 2).

Assessing the effectiveness of gabapentin as an analgesic, there was significant difference in the mean analgesia efficacy out of a total score of 5 (one being the least effective, 5 being the most effective) between fixed vs variable dosing groups (2.9, 95% CI 2.5-3.4 vs 3.8, 95% CI 3.2-4.5; $P = 0.027$). In terms of

Table 1. *Demographics of patient population.*

Age	Patient n (%)
< 60	50 (54.3%)
≥ 60	42 (45.7%)
Gender	
M	35 (38.0%)
W	57 (62.0%)
Pain Location	
Torso	66 (71.7%)
Head and neck	17 (18.5%)
Extremities	9 (9.8%)
Gabapentin Regimen	
Fixed dosing	33 (35.9%)
Variable dosing	12 (13.0%)
Terminated gabapentin	47 (51.1%)
Total n	92 (100%)

Table 2. *Fixed vs variable gabapentin dosing regimen patient characteristics.*

	Fixed Dosing n, mean, ratio (%, 95% CI)	**Variable Dosing n, mean, ratio (%, 95% CI)**	***P* value**
Total n	33	12	
Mean Age	59.2 (53.6-64.9)	65.1 (55.8-74.4)	$P = 0.27$
M:W	1:1.1	5:1	
Analgesia Efficacy	2.9 (2.5-3.4)	3.8 (3.2-4.5)	$P = 0.027$
Satisfaction	3.2 (2.7-3.6)	4.1 (3.40-4.8)	$P = 0.036$
Side Effects	12 (36.4%)	6 (50.0%)	$P = 0.50$
Swelling	0 (0%)	0 (0%)	
Fatigue	2 (6.1%)	3 (25.0%)	
Drowsiness	8 (11.8%)	3 (25.0%)	
Weight gain	1 (3.0%)	0 (0.0%)	
GI upset	0 (0.0%)	1 (8.3%)	
Other*	2 (6.1%)	1 (8.3%)	

CI: confidence interval. *Other side effect: lucid dreams, cognitive impairment, paresthesia.

patients' overall satisfaction taking gabapentin as part of their pain regimen, there was a significant difference between the groups with a higher satisfaction in the variable dosing group compared to the fixed group (4.1, 95% CI 3.4-4.8 vs 3.2, 95% CI 2.7-3.6; $P = 0.036$) (Table 2). There was no difference between the fixed and variable dosing groups with respect to the presence or absence of side effects ($P = 0.50$). In the fixed dosing group, 36.4% of patients experienced side effects, while 50.0% experienced side effects in the variable dosing group. The main side effect experienced in the fixed dosing group was drowsiness with 8 out of 33 (11.8%) patients experiencing drowsiness, and 3 out of 12 (25.0%) experienced drowsiness in the variable dosing group. The other major side effect experienced in the variable dosing group was fatigue with 3 out of 12 (25.0%) patients experiencing fatigue, while only 2 out of 33 (6.1%) experienced fatigue in the fixed dosing group. A single patient complained of weight gain in the fixed dosing group and another of gastrointestinal upset in the variable dosing group. Neither group had any patient that experienced swelling (Table 2).

In those who stopped taking gabapentin, there was no significant difference in the mean age for the fixed and variable dosing groups (57.3, 95% CI 52.6-61.9 years vs 45.8, 95% CI 20.8-70.8 years; $P = 0.12$). The men:women ratio in the fixed group was 1:2.2 and 4:1 in the variable group There was no significant difference between the fixed and variable dosing groups with respect to the presence or absence of side effects ($P > 0.9$). In the fixed dosing group, 47.6% of patients experienced side effects, and 40.0% experienced side effects in the variable dosing group. The main side effect experienced in the fixed dosing group was drowsiness with 12 out of 42 patients experiencing drowsiness, but 2 out of 5 experienced drowsiness in the variable dosing group. A second major side effect in the fixed dosing group was fatigue in which 9 out of 42 experienced and 2 patients in the variable dosing group experienced fatigue. Neither group experienced swelling as a side effect. The main reason for stopping gabapentin in the fixed dosing group was ineffective pain control (54.8%) followed by side effects (21.4%) and improvement of the original pain etiology (21.4%). One patient was concerned about the long-term effects of coming off gabapentin and another described dark thoughts while on the medication. In the variable group, one patient stopped due to side effects, one due to ineffectiveness, and 3 had improvement of the original pain etiology (Table 3).

Discussion

Our retrospective cross-sectional survey revealed an interesting pattern of outcomes as a reflection of the manner of use of gabapentin in patients newly prescribed the drug within the last 2 years. We demonstrated that about a quarter of the patients were using gabapentin on a variable schedule and that patients on a variable gabapentin regimen appeared to rate the medication higher on our scale of efficacy ($P = 0.027$) and experienced greater treatment satisfaction ($P = 0.036$) compared to being on a fixed physician-directed regimen (Table 2). We propose that the rationale behind these findings in our study is a combination of the unique pharmacological characteristics of gabapentin and the individual's processing of painful stimulations in the context of personalized treatment flexibility and autonomy. The lack of significant difference in side effects experienced between the 2 groups ($P = 0.50$) could further suggest achievement of therapeutic balance between efficacy and toxicity in the variable regimen group, revealing a degree of noninferiority in treatment strategy. The favorable assessment of variable gabapentin points to the potential value of gabapentin being used as an as-needed medication. The more favorable perception of self-administered analgesia efficacy in the context of painful insults was also alluded to by Scherer et al (7) who described significantly better pain control and a 97% rate of satisfaction in postpartum women when provided with the option of self-administered medications for analgesia.

Gabapentin, belonging to the gabapentinoid family, is fundamentally characterized as an agent with variable absorption and nonlinear pharmacokinetics, thereby resulting in a high propensity of interindividual variability in plasma concentrations following dosing (8-11). The agent is not protein bound and is completely renally cleared, exhibiting an elimination half-life of 5-7 hours in individuals with normal glomerular filtration rates (8,10,12). Due to this short half-life, it is almost expected to cause significant serum drug concentration fluctuations when dosed once or twice over 24 hours, potentially affecting efficacy and worsening side effects. This is the precise reason why sometimes higher gabapentin doses are prescribed closer to nighttime, while expecting worsening symptoms of dizziness or somnolence to be masked by natural sleep. Due to the inherent nature of the agent described, there are strong proponents of therapeutic serum drug level monitoring for gabapentin in the management of seizures (8,9,13). The complex pharmacology

of gabapentin makes it challenging to ascertain the degree of its analgesic effects solely dependent on a steady serum level of the drug. However, based on the results of our study, steady serum levels as may be seen with fixed dosing may not be as critical to the efficacy of gabapentin. This may suggest that true efficacy of gabapentin is much more closely related to immediate intake of the drug with potential augmentation of the effect through patient autonomy and empowerment in directing their own therapy. Regardless of the inherent mechanism, variable dosing strategy is demonstrated to be therapeutically beneficial in our study.

The measurement and quantification of pain is an exceedingly challenging task. The pursuit of pain improvement as the therapeutic end point reflects only one facet of the multidimensional pain experience. More holistic measures of symptom improvement include indices reflecting physical functionality, quality of life (QoL), as well as overall treatment satisfaction. Therefore, in addition to the raw pharmacological efficacy of gabapentin as a drug, the manner through which therapy was delivered also plays a crucial role in the ultimate perception of treatment success. This observation is built upon the self-determination theory, which suggests that the basic psychological needs for self-autonomy are crucial to the perception of personal well-being (14,15). In the context of our study, the endorsement of patient autonomy is reflected in the independent self-adjusted dosing of gabapentin in the management of chronic pain ailments free of physician intervention. Furthermore, it was found that certain patient attributes, including level of education, severity of illness, and the complexity of information provided, could all contribute to outcomes in patient satisfaction and measures of QoL and function (14,16,17). The chronicity of pain and associated comorbidities in patients from our study pool, as well as the complexity of gabapentin dose determination potentially make our study population most susceptible to large variations in self-measured outcomes of treatment efficacy. We attempted in our study to delineate this correlation between patients' autonomous gabapentin dose adjustment and the overall degree of satisfaction in treatment, as well as the experience of side effects. The limitations within the framework of a pilot study failed to reveal a significant correlation but did provide the impetus for further study in the future.

It is no secret that most gabapentin prescriptions in the United States are for off-label indications and currently 83% of the medication prescribed is for off-label use (18,19). The US Food and Drug Administration (FDA) approval of gabapentin use has not expanded beyond postherpetic neuralgia and epilepsy with partial-onset seizures (18,20). At the time of writing, gabapentin has not been classified as a federally controlled substance by the US Drug Enforcement Agency (20). However, a handful of states (7 over the last 5 years) have made gabapentin a Schedule V controlled substance, with the concern being its consumption when combined with more conventional substances of abuse, such as opioids (21). Given this trend of increased scrutiny over its prescription and use, considerations to afford increased autonomy over its pattern of use may require larger studies in the future to justify such variable usage. Furthermore, the FDA has added a respiratory depression warning to the use of gabapentinoids especially when combined with opioid therapy. Careful education of the risks of gabapentin and parameters of safe use would need to be done if variable dosing is to be prescribed.

Table 3. *Fixed vs variable dosing patient characteristics in patients who stopped taking gabapentin including the mean age, men:women ratio, absence or presence of side effects, and reasons for stopping.*

	Fixed Dosing n, mean, ratio (%, 9%% CI)	**Variable Dosing n, mean, ratio (%, 95% CI)**	***P* value**
Total n	42	5	
Mean Age	57.3 (52.6-61.9)	45.8 (20.8-70.8)	*P* = 0.12
M:W	1:2.2	4:1	
No Side Effects	22 (52.4%)	3 (60%)	*P* > 0.9
Side Effects	20 (47.6%)	2 (40%)	
Swelling	0 (0.0%)	0 (0.0%)	
Fatigue	9 (21.4%)	2 (40.0%)	
Drowsiness	12 (28.6%)	2 (40.0%)	
Weight gain	3 (7.1%)	0 (0.0%?)	
GI upset	1 (2.4%)	1 (20.0%)	
Other*	4 (9.5%)	1 (20.0%)	
Reasons for Stopping			
Ineffective pain control	23 (54.8%)	1 (20.0%)	
Side effects	9 (21.4%)	1 (20.0%)	
Improvement of pain etiology	9 (21.4%)	3 (60.0%)	
Other~	2 (4.8%)	0 (0.0%)	

CI: confidence interval. *Other side effects included light headedness, anorgasmia, palpitations, and hot flashes. ~Other reasons for stopping include anxiety about the medication and long-term effects.

Limitations

Our study is limited by its very nature of being a pilot, single-institution study performed as a cross-sectional survey on a relatively small sample size. Our response rate allowed only a collection of 12 patients who engaged in variable gabapentin use. And despite us not demonstrating a significant difference in side effects sustained, there were numerically a higher number of individuals who suffered from drowsiness and fatigue in the variable dosing group, suggesting that if dosage had been increased sufficiently, that we might be able to observe a notable difference. Additionally, although the results are statistically significant in favor of variable use, the CIs do overlap. A larger study is needed to clarify this significance. A larger prospective study across multiple institutions with clear conveyance of the intention for more than one round of data collection from patients during the initial office visit could significantly improve response and data quality. It is also suggested that face-to-face interviews often result in better response rates and it can also circumvent issues of varying literacy in survey patients (7). Given our focus on patient satisfaction as a crucial endpoint measure, more semi-structured questions could be inserted into future questionnaires to capture qualitative data that the Likert scale questions could not (22). Overall, we envision a much more robust study in the future that allows further breakdown of patient background in collecting data, including, but not limited to. specific pain diagnoses in addition to anatomical demarcation and specific doses and frequency of gabapentin administered.

Medication compliance is an expectation in all patient-doctor relationships and it is certainly not the norm to vary drug doses as it is seen as a clear violation of that contract unless explicitly approved during consultation. None of the patients we surveyed had been given the autonomy to adjust gabapentin doses by their providers and this is believed to significantly reduce the proportion of patients who would otherwise proceed with running a variable dosing regimen. Furthermore, it would also reduce the inherent reluctance of self-reporting home dose adjustments by patients, even when they might already be practicing it, since medication nonadherence had traditionally been interpreted as poor patient conduct.

We attempted, to the best of our abilities, to make clear the distinction between fixed and variable dosing regimens based on the most current dosing practices adopted by patients at the point of contact. However, as most patients were inevitably started on a fixed regimen by their pain physicians through up-titration of gabapentin, this initial escalating regimen can be to some extent considered a variable dosing regimen and limits the reliability of the results; however, the patients had been on gabapentin for at least a month at the time of the interview so traditional titration period would have ended. This classic strategy of dose escalation was clearly demonstrated in both Backonja et al (5) and Rice et al (6) thereby making the therapeutic benefits of gabapentin more challenging to accord as seemingly every patient on a fixed regimen was initially "primed" through a variable regimen. In both of the above studies (5,6), the variable components of the original priming took up at least one-third of the total therapy time. Future studies would need to take this into consideration by clearly defining a lead time of unchanging dosing following the initial variable priming before formally classifying patients to be on a fixed dosing regimen.

Conclusions

Gabapentin is a widely prescribed neuromodulating agent used in multiple indications for neuropathic pain with varying degrees of efficacy. A slow build-up of efficacy and tolerance is presumed based on the studies for diabetic neuropathy and postherpetic neuralgia. However, given the escalatory doses employed in these studies and complex molecular actions of gabapentin, it is not entirely clear how much of this drug's efficacy can be attributed to immediate dosing as opposed to long-term serum levels maintained from chronic use. This pilot study suggests, with identified limitations stated above, improved clinical outcomes in the form of higher agent efficacy and superior patient satisfaction when patients vary their gabapentin regimens. Variable doses did not appear to lead to patients experiencing worsening side effects, or compromise drug safety in this small population. Therefore, the variable dosing option may potentially be considered as an alternative to patients whose lifestyles do not allow for fixed dosing after demonstrating sufficient tolerance to the medication in controlled settings at initiation. Careful education of the risks of gabapentin and parameters of safe use would need to be done if variable dosing is to be prescribed.

A larger prospective study is needed to more accurately assess gabapentin-usage patterns and their associated efficacies in the future to further ascertain our study findings.

References

1. Wiffen PJ, Derry S, Bell RF, et al. Gabapentin for chronic neuropathic pain in adults. *Cochrane Database Syst Rev* 2017; 6:CD007938.
2. van Hecke O, Austin SK, Khan RA, et al. Neuropathic pain in the general population: A systematic review of epidemiological studies. *Pain* 2014; 155:654-662.
3. Kaul I, Amin A, Rosenberg M, et al. Use of gabapentin and pregabalin for pruritus and neuropathic pain associated with major burn injury: A retrospective chart review. *Burns* 2018; 44:414-422.
4. Chang CY, Challa CK, Shah J, et al. Gabapentin in acute postoperative pain management. *Biomed Res Int* 2014; 2014:631756.
5. Backonja M, Beydoun A, Edwards KR, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: A randomized controlled trial. *JAMA* 1998; 280:1831-1836.
6. Rice ASC, Maton S, Postherpetic Neuralgia Study G. Gabapentin in postherpetic neuralgia: A randomised, double blind, placebo controlled study. *Pain* 2001; 94:215-224.
7. Scherer H, Bernier E, Rivard J, et al. Self-Administered medications in the postpartum wards: A study on satisfaction and perceptions. *J Eval Clin Pract* 2017; 23:540-547.
8. Larsen Burns M, Kinge E, Stokke Opdal M, et al. Therapeutic drug monitoring of gabapentin in various indications. Acta Neurol Scand 2019; 139:446-454.
9. Patsalos PN, Spencer EP, Berry DJ. Therapeutic drug monitoring of antiepileptic drugs in epilepsy: A 2018 update. *Ther Drug Monit* 2018; 40:526-548.
10. Bockbrader HN, Wesche D, Miller R, et al. A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. *Clin Pharmacokinet* 2010; 49:661-669.
11. Gidal BE, Radulovic LL, Kruger S, et al. Inter- and intra-subject variability in gabapentin absorption and absolute bioavailability. *Epilepsy Res* 2000; 40:123-127.
12. Patsalos PN, Zugman M, Lake C, et al. Serum protein binding of 25 antiepileptic drugs in a routine clinical setting: A comparison of free non-protein-bound concentrations. *Epilepsia* 2017; 58:1234-1243.
13. Landmark CJ, Johannessen SI, Tomson T. Dosing strategies for antiepileptic drugs: From a standard dose for all to individualised treatment by implementation of therapeutic drug monitoring. *Epileptic Disord* 2016; 18:367-383.
14. Lee YY, Lin JL. Do patient autonomy preferences matter? Linking patient-centered care to patient-physician relationships and health outcomes. *Soc Sci Med* 2010; 71:1811-1818.
15. Ryan RM, Deci EL. On happiness and human potentials: A review of research on hedonic and eudaimonic well-being. *Annu Rev Psychol* 2001; 52:141-166.
16. Ryan J, Sysko J. The contingency of patient preferences for involvement in health decision making. *Health Care Manage Rev* 2007; 32:30-36.
17. Say R, Murtagh M, Thomson R. Patients' preference for involvement in medical decision making: A narrative review. *Patient Educ Couns* 2006; 60:102-114.
18. Campbell LS, Coomer TN, Jacob GK, et al. Gabapentin controlled substance status. *J Am Pharm Assoc* (2003) 2021; 61:e218-e224.
19. Hamer AM, Haxby DG, McFarland BH, et al. Gabapentin use in a managed medicaid population. *J Manag Care Pharm* 2002; 8:266-271.
20. Incorp P. Neurontin [package insert], New York, NY, 2017. www.accessdata.fda.gov/drugsatfda_docs/label/2017/020235s064_020882s047_021129s046lbl.pdf.
21. Eckhardt K, Ammon S, Hofmann U, et al. Gabapentin enhances the analgesic effect of morphine in healthy volunteers. *Anesth Analg* 2000; 91:185-191.
22. Crow R, Gage H, Hampson S, et al. The measurement of satisfaction with healthcare: Implications for practice from a systematic review of the literature. *Health Technol Assess* 2002; 6:1-244.

Appendix 1. *Verbal consent script*.

PI: Jatinder Gill, MD
Pattern Of Gabapentin Consumption
And Predictors Of Efficacy, Adherence
And Adverse Effects

Verbal Consent Script

Version Date: 8/20/21

My name is _____ and I would like to speak to _____. Are you_____?

As I said, my name is _____ and I work with Dr. Jatinder Gill. He is doing a research study on the pattern of gabapentin use for chronic pain after initial prescription. As it is known for patients to self-adjust dosing regimen to achieve the ideal level of pain control, we are interested to find out your pattern of medication use and the associated side effects, overall effectiveness and your satisfaction while on it.

Would you like me to tell you more?

This is a research study, so it may not help you personally if you are in it. We hope that talking to patients like yourself may reveal the most appropriate dosing regimen for gabapentin and the degree of flexibility we should be giving patients directing their pattern of use of the medication. We will interview approximately 100 users of gabapentin such as yourself.

Do you have any questions so far? Would you like to hear more about the study?
If you take part in the study, we'll continue this phone conversation and discuss a questionnaire about your use of gabapentin

The questionnaire will take up to five minutes to complete and this is a one-off survey without future follow-up.
We will use your answers to fill in a written form.

Generally, there are minimal risks to taking part in this study. Your name or identity will not be collected on the questionnaires, and your response cannot be matched to your medical record as the information we gather from you will be kept separate from your medical record. It will only be seen by Dr. Gill and people like me who are helping him with this study. To protect your privacy, we will not put your name on any of these study papers.

We may report on the study at meetings or in written articles. If we do that, we will never use your name or any other information that would show that you were in the study.

It will not cost you any money to be in this study, and we will not compensate you for your time.

Appendix 1 cont. *Verbal consent script*.

Participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled. You can discontinue participation at any time without penalty or loss of benefits, to which you are otherwise entitled

If you have any questions before, during, or after the study, you can ask me, Dr. Gill, or anyone else working on this. You can also contact someone in the BIDMC Human
Subject Protection Office (617 - 975 - 8500) if you have questions about your rights when you take part in research.

Do you want to volunteer to be in this study?

~~~~~~~~~~~~~~~end~~~~~~~~~~~~~~~

Subject Consented? ☐ Yes (Name: _____) ☐ No (reason: _____)
~~~~~~~~~~~~~~~

Appendix 2. *Gabapentin questionnaire.*

PI: Jatinder Gill, MD
Pattern Of Gabapentin Consumption
And Predictors Of Efficacy, Adherence
And Adverse Effects

Subject Telephone Interview Script

Version Date: 10/29/21

Are you taking gabapentin?

If Yes:

(a) Are you taking the same dose of gabapentin everyday or are you varying the doses?

(i) If same dose (Fixed dosing):

(1) Is it effective in controlling your pain?

1. □ Not at All Effective
2. □ A Little Effective
3. □ Somewhat Effective
4. □ Very Effective
5. □ Extremely Effective

(2) Are you experiencing adverse effects and if you are, what are they?

1. □ Swelling
2. □ Fatigue
3. □ Drowsiness
4. □ Weight gain
5. □ GI upset
6. □ Other: _____

(3) How satisfied are you on this fixed dose drug regimen?

1. □ Not at All Satisfied
2. □ A Little Satisfied
3. □ Somewhat Satisfied
4. □ Very Satisfied
5. □ Extremely Satisfied

(ii) If varying dose (Variable dosing):

(1) What made you vary the gabapentin dose? _____

(2) Is it effective in controlling your pain?

Appendix 2 cont. *Gabapentin questionnaire.*

1. □ Not at All Effective
2. □ A Little Effective
3. □ Somewhat Effective
4. □ Very Effective
5. □ Extremely Effective

(3) Are you experiencing adverse effects and if you are, what are they?

1. □ Swelling
2. □ Fatigue
3. □ Drowsiness
4. □ Weight gain
5. □ GI upset
6. □ Other: _____

(4) How satisfied are you on this variable dose drug regimen?

1. □ Not at All Satisfied
2. □ A Little Satisfied
3. □ Somewhat Satisfied
4. □ Very Satisfied
5. □ Extremely Satisfied

If No:

(b) Have you been on gabapentin for more than 1 month prior to stopping?

(c) What was the reason gabapentin was stopped? _____

(d) Did you experience adverse effects and if you were, what were they?

1. □ Swelling
2. □ Fatigue
3. □ Drowsiness
4. □ Weight gain
5. □ GI upset
6. □ Other: _____

(e) Were you previously on a fixed or variable dosing regimen?

Appendix 2 cont. ***Gabapentin questionnaire***.

1. □ Yes
2. □ No

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