PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Patterns of pregabalin prescribing in four German federal states: analysis of routine data to investigate potential misuse of pregabalin
AUTHORS	Flemming, Ronja

VERSION 1 – REVIEW

REVIEWER	Ong, Mei-Sing Harvard University
REVIEW RETURNED	29-Jan-2022

GENERAL COMMENTS	This study applied social network analysis to characterize patterns of pregabalin misuse across 4 states in Germany. The study explores an important public health issue and has the potential to offer unique insights into the drivers of prescription drug abuse. I believe the paper can be substantially strengthened if the author can address the following concerns. 1. “Intentional pregabalin misuse” has been defined as pregabalin use exceeding 600mg/day. As the author rightly pointed out, the administrative dataset used in the study does not provide reasons for pregabalin use. There may be other reasons for prescription of >600mg/day pregabalin, e.g. variation in practice among clinicians, fragmented care leading to unintentional over-prescription. Thus, the assumption that an individual who was prescribed >600mg/day of pregabalin must be engaged in doctor-shopping or pregabalin abuse may not be valid. This limitation should be discussed and the conclusions drawn from the analysis should be toned down appropriately. Additional sensitivity analyses can also be performed to differentiate those who were prescribed >600mg/day by a single provider vs multiple providers. 2. Extended release form of pregabalin can be prescribed up to 660mg/day. Has the study considered that? Please also report the average and range of pregabalin dose/day among normal users vs “misusers”. 3. Overall, the study and the interpretation of its findings can be better informed by the clinical contexts in which pregabalin can be prescribed. E.g. the study found that patients prescribed with benzodiazepines within the year prior to the initial pregabalin prescription were more likely to “misuse” pregabalin. Pregabalin can be used as adjunctive therapy in the discontinuation of benzodiazepine, though this practice is controversial. So, use of pregabalin among patients on benzodiazepine may be clinically warranted and does not necessarily indicate misuse. Pregabalin is also sometimes used concomitantly with opioids in the treatment of chronic pain. It would be important to have the manuscript reviewed by a clinical expert in the field.

	4. Can the author comment on the completeness of the data? Did all patients have at least one year of lead-up and follow-up period before/after the initial prescription of pregabalin? If not, there may be issue with confounding by indication. Specifically, prolonged use of pregabalin can lead to addiction and substance use disorder (SUD). Patients with SUD are also more likely to have chronic pain. So, the relationship between SUD and use of pregabalin may not reflect misuse. It may not be possible to tease out all these factors given the nature of the dataset. But a discussion of the limitations is warranted, and again, input from clinical experts would be important. 5. Many of the factors associated with pregabalin use were likely to be inter-dependent. It would be useful to conduct multivariate analyses to evaluate which factors are most predictive. 6. Descriptive analyses of which patient subgroups were more likely to have lower care density (and hence more likely to experience poor coordination of care) would be useful. 7. Please specify if the study has been approved by the appropriate ethics committee.

REVIEWER	Reviewer 2: Ponton, R The University of Auckland, School of Pharmacy
REVIEW RETURNED	23-Feb-2022

GENERAL COMMENTS	Thank you for the opportunity to review this interesting manuscript. On the whole, it presents some succinct information regarding the potential misuse of pregabalin. It adds to the body of information detailing pregabalin misuse, but has some flaws that need to be addressed or described prior to publication. High level data, whilst accessible and presenting large numbers of cases, has limitations and these need to be recognised and detailed in such publications: it is not the 'be all and end all' of prescribing analysis. Further work reviewing patient-level data (prescriber records) should be recommended to confirm the assumptions and discussions drawn in such high-level analyses. The main issue that needs to be addressed before publication are some aspects of assumption, most importantly that of frequent prescription pick-up indicating increased pregabalin dose. This is likely, but remains an assumption. Some level of tolerance could be applied to what is defined as 'excessive'. See further details below. Specific issues to address: The manuscript title could potentially be improved (and simplified) to better describe the work. Misuse and abuse used interchangeably - consider 'substance use' instead or change to consistent term 'misuse' (except where not possible, such as in reference term) Suggest use of British English for use in British Medical Journal (including spellings such as 'behavioral' and use of 'z' instead of 's' such as 'analyze', 'organization') Specific comments:

	Page 4 (proof document page number), Line 51: 'middle aged men' should be qualified: what age range does this encompass? Use this age range rather than an unclear term P5: Are the patient population potentially more liable to substance use? i.e. does the German insurance system cover unemployed or more deprived populations, or is this insurance that is 'paid for' and relates more to employed individuals with the ability to afford such cover. P5, L42: Word 'have' is missing ("should not have been") P5, L47: is there a relevance to "and reimbursed"? The collection of the dispensed ('filled') medicine is assumedly most important in description of drug use P5: Definition of potential misuse section - this is key to this work. This is an area where I too have struggled to define what is 'excessive'. It appears that you have assessed any dispensing of drug to enable consumption of a dose of 600mg per day as misuse. Whilst crude, this arbitrary cut-off seems well defined, however there is some potential for 'false positives' in the situations where patients may obtain prescriptions slightly early to gain some spare drug for 'safe-keeping' at home, whilst actually not taking excessive doses. Did you account for any "acceptable" excess? Either way, this might need to be clarified for the reader. Referral to a paper can be offered if wished. In addition, does the German prescribing system lead to prescribing of other drugs on the same prescription? For example, if someone was misusing an opioid on the same prescription as the pregabalin and getting repeated prescriptions early to obtain the opioid (with pregabablin co-prescribed, but not consuming the pregabalin to excess) P6, L59: "Psychostimulants" could be expanded to describe the drugs that the authors have placed in this class and that are available on prescription in Germany P8, L11: Reference error P9, L21: Be careful of the use of the term 'normal users' - this cannot be assumed (they could use in binges), and it creates stigmatization between the two groups. Suggest 'those taking pregabalin as prescribed' or similar. Address this throughout manuscript as well as at this instance. P9, L38: Recommend not referring to substance use disorder as 'disease' (and in any other potential instances in manuscript) P10, Table 2: 'Approved Indication' - where none is stated this suggests that the patient has no appropriate indication. I believe the authors mean 'not specified or recorded in records' for the most part - as opposed to patient having been prescribed the drug for no reason. P11, L6: Adjust opening sentence - 'The presented study...' or simply 'This study...' P11, L30: There is a significant issue raised here: previously (as highlighted above) pregabalin users were stated to be 'middle-

	aged' (including in abstract), but at this point in manuscript, the term younger men is used. This needs to be addressed and corrected, ideally with age ranges specified for clarity and remove ambiguity of terms such as 'younger' and 'middle-aged'. P11, L37: Pregabalin misuse alone may be unexpected to the authors, but it is not to anyone who has worked clinically with this drug: misuse and/or dependence can occur with any drug, irrespective of other drug consumption or not. P11, L44: This is a very big assumption - as stated. Given the lack of specific data, it is hard to justify discussing this. P12, L18: 'misusing patients' - this term is inappropriate and does not denote a person potentially misusing a drug (a physician could 'misuse' a patient) P12, L42: Whilst this measure may be conservative for most patients, it will contain a small number of false positives. As stated above, this should be recognised. The discussion/conclusions demonstrate and reiterate the well known (and expected) need for clinicians to communicate and The manuscript may be served well to include a sentence or two on any prescription restrictions or controls on pregabalin in the localities studied; for example, some countries/states treat pregabalin as a controlled drug. Is this the case in Germany? If not, this should be outlined, potentially in the discussion? The abstract should be updated and revised thoroughly accordingly to accommodate changes in the body of the manuscript.

REVIEWER	Schaffer, Andrea University of New South Wales, Centre for Big Data Research in Health
REVIEW RETURNED	08-Mar-2022

GENERAL COMMENTS	This manuscript describes a study of people with >=3 prescriptions of pregabalin, and compares characteristics of people using an average daily dose of <=600 mg or >600 mg. This is primarily a descriptive study, but also incorporates network analysis to identify links between prescribers to these two groups. There are some interesting data here, and I have a few questions and comments. 1. When describing the data the authors state, “The AOK insures about 42% of the population in these regions, and the insured population differs only slightly from the general German population in terms of age and gender.[20] The provided dataset covered about 14% of their insured population from the years 2013 to 2017.” I just want to make sure I understand this correctly, does this mean the data comprised 14% of the 42%? So ~6% of the population? 2. I don’t think calling people taking <=600 mg per day “normal users” is the best choice of terminology (especially since people taking <=600 mg may still be misusing pregabalin). I suggest using something more specific, such as “users of therapeutic doses” or something similar.

	3. The authors should be careful in interpreting their results, as the study only includes people with >=3 prescriptions and cannot be generalised to all pregabalin users. According to Figure 1, the majority of pregabalin users were excluded (59%) for having received <3 prescriptions. For instance, when the authors state in the Discussion “The proportion of patients misusing pregabalin amounted to 1.7% in our sample,” I suggest making it clear that this is only 1.7% of people with >=3 prescriptions (and so a much smaller proportion of all pregabalin users). This has implications when comparing this estimate to other studies, which may have been based on the full population of pregabalin users. 4. Related to the above, in the Abstract please state that the population was people with >=3 prescriptions over one year. 5. An important limitation not addressed in the Discussion is that this study focusses on one aspect of misuse only (excessive daily dose). However, there are other ways to misuse pregabalin, such as combined with one or more other sedative medicines (e.g. opioids, benzodiazepines). 6. The authors refer to the “prescribed average daily dose” when defining misuse. However, the daily dose was inferred based on the total quantity dispensed. Thus, this is different than the “prescribed” dose, since people may be taking excessive doses differently from how it was prescribed. Therefore I suggest dropping the qualifier “prescribed” and just refer to “average daily dose.” 7. The authors state they focussed only on pregabalin (not gabapentin) since it has more abuse potential. However, there are also concerns about misuse of gabapentin in some jurisdictions where gabapentin is more common than pregabalin (e.g. USA). If the authors wish to focus on pregabalin only, it would still be useful to see how many people were also prescribed gabapentin in Table 2. 8. The authors state in the Discussion that “relatively few patients misusing pregabalin had a prior medication with opioids.” I don't think I'd say "few" patients, as 41% of pregabalin “misusers” had been prescribed opioids. Opioids and pregabalin are both used to treat pain, so it makes sense that their use is high in both “normal” users and “misusers," especally given the belief that gabapentinoids combined with opioids have an “opioid-sparing” effect. 9. In Table 1, What is the difference between “neuropathic pain-related diagnoses” and “additional neuropathic pain-related diagnoses (broad pattern)”? 10. I’m curious about inclusion of I69.1 (sequelae of intracerebral haemorrhage) and I69.3 (sequelae of cerebral infarction) under “neuropathic pain-related diagnoses.” How are these neuropathic pain related? 11. In Table 2, please only provide one p-value for categorial variables (e.g. age), since they should be tested as a whole. It appears that the authors just copy and pasted the p-values for

	each category, but this is not a standard approach and is confusing. 12. Is the “adjusted p-value” in Table 2 the Bonferroni adjusted value? If so this should be explicitly stated in the table. 13. The authors state that since this is a secondary data analysis no ethics approval was needed. In my jurisdiction this sort of analysis would require ethics approval since it contains potentially re-identifiable information (age, sex, geographic region, medical records, etc).

VERSION 1 – AUTHOR RESPONSE

Reviewer 1		
R1.1	“Intentional pregabalin misuse” has been defined as pregabalin use exceeding 600mg/day. As the author rightly pointed out, the administrative dataset used in the study does not provide reasons for pregabalin use. There may be other reasons for prescription of >600mg/day pregabalin, e.g. variation in practice among clinicians, fragmented care leading to unintentional over-prescription. Thus, the assumption that an individual who was prescribed >600mg/day of pregabalin must be engaged in doctor-shopping or pregabalin abuse may not be valid. This limitation should be discussed and the conclusions drawn from the analysis should be toned down appropriately. Additional sensitivity analyses can also be performed to differentiate those who were prescribed >600mg/day by a single provider vs multiple providers.	Thank you very much for this advice. It is important to highlight that there are multiple reasons for patients exceeding this amount of 600mg/day pregabalin on their prescriptions and obviously not all of them are misusing the drug. I revised the manuscript and tried not to categorically label the group of patients with a high prescription volume as misusers and to better express that they are only possibly misusers. Additionally, I worked on the discussion section to better address this relevant issue. Additionally, I added a sensitivity analysis in which I differentiated the group of patients with high doses of pregabalin in those who were prescribed by a single provider and those with multiple providers and addressed the results in the discussion section.
R1.2	Extended release form of pregabalin can be prescribed up to 660mg/day. Has the study considered that? Please also report the average and range of pregabalin dose/day among normal users vs “misusers”.	Thanks for this advice. To my knowledge, there is no extended release form of pregabalin approved and available on the German drug market. Therefore, this higher dosage should not be prescribed.
R1.3	Overall, the study and the interpretation of its findings can be better informed by the clinical contexts in which pregabalin can be prescribed. E.g. the study found that patients prescribed with benzodiazepines within the year prior to the initial pregabalin prescription were more likely to “misuse” pregabalin. Pregabalin can be used as	I thank you for this good objection and the advice. The discussion section has been updated with respect to the clinical application possibilities of pregabalin. However, it should be considered that also in light of these additional application possibilities the patients should still not be

	adjunctive therapy in the discontinuation of benzodiazepine, though this practice is controversial. So, use of pregabalin among patients on benzodiazepine may be clinically warranted and does not necessarily indicate misuse. Pregabalin is also sometimes used concomitantly with opioids in the treatment of chronic pain. It would be important to have the manuscript reviewed by a clinical expert in the field.	treated with dosages above the maximum of 600mg/day.
R1.4	Can the author comment on the completeness of the data? Did all patients have at least one year of lead-up and follow-up period before/after the initial prescription of pregabalin? If not, there may be issue with confounding by indication. Specifically, prolonged use of pregabalin can lead to addiction and substance use disorder (SUD). Patients with SUD are also more likely to have chronic pain. So, the relationship between SUD and use of pregabalin may not reflect misuse. It may not be possible to tease out all these factors given the nature of the dataset. But a discussion of the limitations is warranted, and again, input from clinical experts would be important.	The inclusion of patients was conducted considering these two aspects. It is ensured that both a lead-up and a follow-up year were available for all patients. Thank you for the query, I have now clearly described this point in the methods section. The paper was revised in order to better highlight that the group of patients with a large prescription amount of pregabalin, does not necessarily exclusively contain misusers. Thus, the multiple causes should now be better described (see also reviewer comment and answer 1.1).
R1.5	Many of the factors associated with pregabalin use were likely to be inter-dependent. It would be useful to conduct multivariate analyses to evaluate which factors are most predictive.	Thank you very much for this suggestion. It is a very important note that the presented results are descriptive only. The analyses were intended to show exploratively to whom and by whom what quantities of pregabalin are prescribed, so univariate statistics were chosen. However, in further studies it is certainly very important to investigate which of the factors are most predictive.
R1.6	Descriptive analyses of which patient subgroups were more likely to have lower care density (and hence more likely to experience poor coordination of care) would be useful.	Thank you very much for this advice. This study was meant to explore the prescription situation of pregabalin. It was shown that patients with a high prescription volume of pregabalin experienced a lower care density. I agree that it would also be interesting to analyse in detail what patient groups are more likely to have a lower care density. Since this approach would change the aim of the study, I think that this should be done in another study.

R1.7	Please specify if the study has been approved by the appropriate ethics committee.	There was no approval by an ethics committee but the following Ministries in their role as supervisory authorities of the statutory health insurances in the regions approved the utilization of the data: Bavarian State Ministry for Health and Care, Hessian Ministry for Social Affairs and Integration and Saxon State Ministry for Social Affairs and Consumer Protection. The legal basis for the processing was given by the section 75 of Book X of the German Code of Social Law. By contract, it was excluded that conclusions are drawn on individual patients and only aggregated results are presented.
Reviewer 2		
	Thank you for the opportunity to review this interesting manuscript. On the whole, it presents some succinct information regarding the potential misuse of pregabalin. It adds to the body of information detailing pregabalin misuse, but has some flaws that need to be addressed or described prior to publication. High level data, whilst accessible and presenting large numbers of cases, has limitations and these need to be recognised and detailed in such publications: it is not the 'be all and end all' of prescribing analysis. Further work reviewing patient-level data (prescriber records) should be recommended to confirm the assumptions and discussions drawn in such high-level analyses.	Thank you very much for your comment on the manuscript. The high level routine data combine advantages and clear disadvantages. Routine data lack important information about reasons for prescriptions, information about actually consumed quantities of a drug and consequently reasons for high prescribed volumes of a drug are also not available. However, from a patient perspective they depict the only possible way to get complete information about dispensed prescriptions from different providers since this information is not stored elsewhere in Germany. Nevertheless, to confirm the assumptions one would need to conduct a clinical study including patients and all their health care providers in order to get the lacking information.
R2.1	The manuscript title could potentially be improved (and simplified) to better describe the work.	The title has been revised and changed in order to better reflect what was done in the study.
R2.2	Misuse and abuse used interchangeably - consider 'substance use' instead or change to consistent term 'misuse' (except where not possible, such as in reference term)	Thank you very much for this advice. I revised the manuscript and followed the definitions for “abuse” and “misuse” given in the publication by *Smith SM, Dart RC, Katz NP, et al. Classification and definition of misuse, abuse, and related events in clinical trials: ACTTION systematic review*

		and recommendations. Pain. 2013;154:2287–96 PubMed . I have decided to use "misuse" in the manuscript, since there is no information about the cause/intention for the high prescription amounts. In the cited studies on pregabalin, however, "abuse" is mentioned very frequently and, to my understanding, often corresponds to the given definition. Pregabalin is intentionally consumed in higher amounts to achieve a euphoric or sedative state.
R2.3	Suggest use of British English for use in British Medical Journal (including spellings such as 'behavioral' and use of 'z' instead of 's' such as 'analyze', 'organization')	Thanks for this suggestion. The manuscript has been changed to British English.
R2.4	Page 4 (proof document page number), Line 51: 'middle aged men' should be qualified: what age range does this encompass? Use this age range rather than an unclear term	The wordings “middle aged men” and “younger men” have been replaced with the age ranges meant by these terms. (see also reviewer comment R2.15)
R2.5	P5: Are the patient population potentially more liable to substance use? i.e. does the German insurance system cover unemployed or more deprived populations, or is this insurance that is 'paid for' and relates more to employed individuals with the ability to afford such cover.	Thank you very much for your query giving me the possibility to refer to that issue in the manuscript. In Germany, about 90% of the population is insured with a statutory health insurance, leading to an approximately representative population. With regard to the health insurance company studied (AOK), it can be stated that its insured persons show only slight deviations in terms of age and gender.
R2.6	P5, L42: Word 'have' is missing ("should not have been")	Thank you, the word “have” has been added.
R2.7	P5, L47: is there a relevance to "and reimbursed"? The collection of the dispensed ('filled') medicine is assumedly most important in description of drug use	Yes, that is correct. Thank you for the remark. The manuscript has been revised accordingly.
R2.8	P5: Definition of potential misuse section - this is key to this work. This is an area where I too have struggled to define what is 'excessive'. It appears that you have assessed any dispensing of drug to enable consumption of a dose of 600mg per day as misuse. Whilst crude, this arbitrary cut-off seems well defined, however there is some	Thank you for the comment on this important issue. First, I have added references, using a similar cut-off. Additionally, I recognized that the issue of classifying “false positives” was not sufficiently discussed in the paper. Therefore, I have revised the discussion section to address this aspect.

	potential for 'false positives' in the situations where patients may obtain prescriptions slightly early to gain some spare drug for 'safe-keeping' at home, whilst actually not taking excessive doses. Did you account for any "acceptable" excess? Either way, this might need to be clarified for the reader. Referral to a paper can be offered if wished. In addition, does the German prescribing system lead to prescribing of other drugs on the same prescription? For example, if someone was misusing an opioid on the same prescription as the pregabalin and getting repeated prescriptions early to obtain the opioid (with pregabablin co-prescribed, but not consuming the pregabalin to excess)	This approach would be technically feasible and can be added to the list of multiple reasons for a large amount of prescribed pregabalin. The variety of causes was described in more detail in the discussion section, clarifying that not all of the patients are in fact misusing pregabalin.
R2.9	P6, L59: "Psychostimulants" could be expanded to describe the drugs that the authors have placed in this class and that are available on prescription in Germany	The three categories of drugs, which are included in the ATC of the “Psychostimulants”, have been named in the manuscript and the reference to access the full list of German ATC codes has been added.
R2.10	P8, L11: Reference error	Thank you, the error has been corrected.
R2.11	P9, L21: Be careful of the use of the term 'normal users' - this cannot be assumed (they could use in binges), and it creates stigmatization between the two groups. Suggest 'those taking pregabalin as prescribed' or similar. Address this throughout manuscript as well as at this instance.	Thank you for this feedback. Since the term (“normal users”) seems to stigmatize too much, I revised the paper and used another wording instead of “normal users”.
R2.12	P9, L38: Recommend not referring to substance use disorder as 'disease' (and in any other potential instances in manuscript)	Thank you for this advice. The manuscript has been revised accordingly.
R2.13	P10, Table 2: 'Approved Indication' - where none is stated this suggests that the patient has no appropriate indication. I believe the authors mean 'not specified or recorded in records' for the most part - as opposed to patient having been prescribed the drug for no reason.	Yes, that is the right interpretation. Thank you for giving me the possibility to clarify this aspect in the table and in the manuscript.
R2.14	P11, L6: Adjust opening sentence - 'The presented study...' or simply 'This study...'	The error has been corrected.

R2.15	P11, L30: There is a significant issue raised here: previously (as highlighted above) pregabalin users were stated to be 'middle-aged' (including in abstract), but at this point in manuscript, the term younger men is used. This needs to be addressed and corrected, ideally with age ranges specified for clarity and remove ambiguity of terms such as 'younger' and 'middle-aged'.	The wordings “middle aged men” and “younger men” have been replaced with the age ranges meant by these terms. (see also reviewer comment R2.4)
R2.16	P11, L37: Pregabalin misuse alone may be unexpected to the authors, but it is not to anyone who has worked clinically with this drug: misuse and/or dependence can occur with any drug, irrespective of other drug consumption or not.	Thanks for this remark. I intended to highlight that the results were unexpected with respect to other studies in which it was shown that patients with an opioid addiction might also abuse pregabalin. The paragraph has been rewritten.
R2.17	P11, L44: This is a very big assumption - as stated. Given the lack of specific data, it is hard to justify discussing this.	Thank you for this advice. The discussion section has been revised and especially the clinical application possibilities of Pregabalin were discussed in more detail. Thus, this paragraph was changed.
R2.18	P12, L18: 'misusing patients' - this term is inappropriate and does not denote a person potentially misusing a drug (a physician could 'misuse' a patient)	Thanks for this correction. It has been adopted.
R2.19	P12, L42: Whilst this measure may be conservative for most patients, it will contain a small number of false positives. As stated above, this should be recognised.	Thank you for this advice. The issue of “false positives” has been addressed in more detail in the discussion section.
R2.20	The discussion/conclusions demonstrate and reiterate the well known (and expected) need for clinicians to communicate and	
R2.21	The manuscript may be served well to include a sentence or two on any prescription restrictions or controls on pregabalin in the localities studied; for example, some countries/states treat pregabalin as a controlled drug. Is this the case in Germany? If not, this should be outlined, potentially in the discussion?	Thank you very much for this query. Except for guidelines that address economic aspects of prescriptions (generic prescribing), there are no prescribing restrictions for pregabalin. In Germany, only narcotics are treated separately and their prescription quantities are monitored. Since pregabalin is not a narcotic, there is no monitoring of prescription quantities. This aspect was better emphasized in the introduction.
R2.22	The abstract should be updated and revised thoroughly accordingly to accommodate changes in the body of the manuscript.	Thank you, the abstract has been updated.

Reviewer 3		
	When describing the data the authors state, “The AOK insures about 42% of the population in these regions, and the insured population differs only slightly from the general German population in terms of age and gender.[20] The provided dataset covered about 14% of their insured population from the years 2013 to 2017.” I just want to make sure I understand this correctly, does this mean the data comprised 14% of the 42%? So ~6% of the population?	Yes, that is the correct conclusion. However, it is important to note that the dataset includes all patients of the regions who are insured with the AOK and who received at least one prescription of pregabalin.
	I don’t think calling people taking <=600 mg per day “normal users” is the best choice of terminology (especially since people taking <=600 mg may still be misusing pregabalin). I suggest using something more specific, such as “users of therapeutic doses” or something similar.	Thank you for this feedback. The term “normal users” was changed throughout the manuscript (see also Reviewer comment R2.11)
	The authors should be careful in interpreting their results, as the study only includes people with >=3 prescriptions and cannot be generalised to all pregabalin users. According to Figure 1, the majority of pregabalin users were excluded (59%) for having received <3 prescriptions. For instance, when the authors state in the Discussion “The proportion of patients misusing pregabalin amounted to 1.7% in our sample,” I suggest making it clear that this is only 1.7% of people with >=3 prescriptions (and so a much smaller proportion of all pregabalin users). This has implications when comparing this estimate to other studies, which may have been based on the full population of pregabalin users.	Thank you very much for this comment. It is important for interpreting the results that I only included patients with >= 3 prescriptions leading to a clearly smaller amount of patients. Comparing the results with other studies has to be done with respect to this technical detail. I checked the references and revised the manuscript accordingly.
	Related to the above, in the Abstract please state that the population was people with >=3 prescriptions over one year.	Thank you for this remark. The abstract has been changed accordingly.
	An important limitation not addressed in the Discussion is that this study focusses on one aspect of misuse only (excessive daily dose). However, there are other ways to misuse pregabalin, such as combined with	Thank you very much for this important aspect. The limitations were amended by this issue.

	one or more other sedative medicines (e.g. opioids, benzodiazepines).	
	The authors refer to the “prescribed average daily dose” when defining misuse. However, the daily dose was inferred based on the total quantity dispensed. Thus, this is different than the “prescribed” dose, since people may be taking excessive doses differently from how it was prescribed. Therefore I suggest dropping the qualifier “prescribed” and just refer to “average daily dose.”	Thank you very much for this suggestion. In the manuscript, I now refer to “average daily dose”.
	The authors state they focussed only on pregabalin (not gabapentin) since it has more abuse potential. However, there are also concerns about misuse of gabapentin in some jurisdictions where gabapentin is more common than pregabalin (e.g. USA). If the authors wish to focus on pregabalin only, it would still be useful to see how many people were also prescribed gabapentin in Table 2.	Thank you very much for this good suggestion. Another variable was added to the list, presenting the amount of patients with at least one prescription gabapentin during the observation period.
	The authors state in the Discussion that “relatively few patients misusing pregabalin had a prior medication with opioids.” I don't think I'd say "few" patients, as 41% of pregabalin “misusers” had been prescribed opioids. Opioids and pregabalin are both used to treat pain, so it makes sense that their use is high in both “normal” users and “misusers," especally given the belief that gabapentinoids combined with opioids have an “opioid-sparing” effect.	Thank you very much for this comment. The phrase “relatively few” was meant to compare the two groups, since the group with lower doses of pregabalin included a higher amount of patients with a prescription for opioids than the group of patients potentially misusing pregabalin. The paragraph has been changed in order to better express this aspect. Additionally, I added the important clinical aspect giving a possible explanation for the high amount of patients receiving both opioids and pregabalin.
	In Table 1, What is the difference between “neuropathic pain-related diagnoses” and “additional neuropathic pain-related diagnoses (broad pattern)”?	The difference concerns the ICD-10 codes taken into account in each case (see Table 1). The broader pattern was used to include more imprecise diagnoses, which might occur in the ambulatory sector. However, the results do not show any differences between the groups.
	I’m curious about inclusion of I69.1 (sequelae of intracerebral haemorrhage) and I69.3 (sequelae of cerebral infarction)	Thank you very much for this query. As to my knowledge, one possible sequelae of intracerebral haemorrhage and cerebral infarction is (neuropathic) pain. In order to

	under “neuropathic pain-related diagnoses.” How are these neuropathic pain related?	include most possible diagnoses for prescription of pregabalin, these diagnoses were added to the list.
	In Table 2, please only provide one p-value for categorial variables (e.g. age), since they should be tested as a whole. It appears that the authors just copy and pasted the p-values for each category, but this is not a standard approach and is confusing.	Thank you very much for this hint. The table has been corrected.
	Is the “adjusted p-value” in Table 2 the Bonferroni adjusted value? If so this should be explicitly stated in the table.	The adjusted p-values are the Bonferroni adjusted p-values and this is now stated in the table. Thank you for this advice.
	The authors state that since this is a secondary data analysis no ethics approval was needed. In my jurisdiction this sort of analysis would require ethics approval since it contains potentially re-identifiable information (age, sex, geographic region, medical records, etc).	There was no approval by an ethics committee but the following Ministries in their role as supervisory authorities of the statutory health insurances in the regions approved the utilization of the data: Bavarian State Ministry for Health and Care, Hessian Ministry for Social Affairs and Integration and Saxon State Ministry for Social Affairs and Consumer Protection. The legal basis for the processing was given by the section 75 of Book X of the German Code of Social Law. By contract, it was excluded that conclusions are drawn on individual patients and only aggregated results are presented.

VERSION 2 – REVIEW

REVIEWER	Ong, Mei-Sing Harvard University
REVIEW RETURNED	15-Jun-2022

GENERAL COMMENTS	Thanks you for addressing the concerns raised in my previous review. Several minor comments: 1. In abstract: Methods section should specify how the study defines higher than medically recommended pregabalin dose (i.e. >600mg/day). 2. The author should clarify in the manuscript why ethics approval was not required for the study.

	3. The author described care density as “a summary value of cooeraptign among physicians”. A more accurate definition is “a surrogate measure of care coordination”. Care density may not be a concept that readers are familiar with. It would be helpful to elaborate on the concept, citing studies that defined the concept.

REVIEWER	Ponton, R The University of Auckland, School of Pharmacy
REVIEW RETURNED	23-Jun-2022

GENERAL COMMENTS	Thank you for revising the manuscript in accordance with the previous reviewer's comments, including those I provided. Despite the changes, I feel the manuscript could benefit from some editing to improve readability and, in particular, express the science in the most efficient and clear manner. Title: Recommend further improvement to improve readability, suggest: ‘Patterns of pregabalin prescribing in four German federal states: analysis of routine prescribing data to identify patients potentially misusing pregabalin' - but I will leave you as the author to decide the title for your manuscript. Throughout paper: The phrase ‘pregabalin users’ could be corrected to ‘people who use pregabalin’ or ‘people prescribed pregabalin’; the former can be considered stigmatising and dehumanising. Page 9: Results “In total, 53,049 patients accounting for less than 1% of the population” The wording of this sentence that the small percentage of the population is inconsequential. I am sure that is not the intention of the author. Remove the percentage remark? Or make it precise and simply place in brackets? E.g. “53,049 patients (0.xxx% of the locality population)….”

REVIEWER	Schaffer, Andrea University of New South Wales, Centre for Big Data Research in Health
REVIEW RETURNED	06-Jun-2022

GENERAL COMMENTS	I am satisfied with how the authors have addressed my comments.

VERSION 2 – AUTHOR RESPONSE

R1.1	In abstract: Methods section should specify how the study defines higher than medically recommended pregabalin dose (i.e. >600mg/day).	Thank you very much for this advice, the specification of classification was added to the abstract.

R1.2	The author should clarify in the manuscript why ethics approval was not required for the study.	Thank you for this advice. The Ethics approval section has been updated and includes the requested information now.
R1.3	The author described care density as “a summary value of cooeraptign among physicians”. A more accurate definition is “a surrogate measure of care coordination”. Care density may not be a concept that readers are familiar with. It would be helpful to elaborate on the concept, citing studies that defined the concept.	Thank you very much for this more accurate definition. It has been updated in the manuscript. Additionally, references were added.
R2.1	Title: Recommend further improvement to improve readability, suggest: ‘Patterns of pregabalin prescribing in four German federal states: analysis of routine prescribing data to identify patients potentially misusing pregabalin' - but I will leave you as the author to decide the title for your manuscript.	Thank you for your suggestion to change the title of the manuscript. I have adopted part of the suggested title.
R2.2	Throughout paper: The phrase ‘pregabalin users’ could be corrected to ‘people who use pregabalin’ or ‘people prescribed pregabalin’; the former can be considered stigmatising and dehumanising.	Thank you very much for this idea of changing the phrase “pregabalin users”. This has been updated throughout the paper
R2.3	Page 9: Results “In total, 53,049 patients accounting for less than 1% of the population” The wording of this sentence that the small percentage of the population is inconsequential. I am sure that is not the intention of the author. Remove the percentage remark? Or make it precise and simply place in brackets? E.g. “53,049	Thank you for this advice. The sentence has been changed.

	patients (0.xxx% of the locality population)….”	