PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (http://bmjopen.bmj.com/site/about/resources/checklist.pdf) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Understanding and reducing the prescription of hypnotics and sedatives at the interface of hospital care and general practice: A protocol for a mixed-methods study</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUTHORS</td>
<td>Heinemann, Stephanie; Weiß, Vivien; Straube, Kati; Nau, Roland; Grimmsmann, Thomas; Himmel, Wolfgang; Hummers-Pradier, Eva</td>
</tr>
</tbody>
</table>

VERSION 1 - REVIEW

| REVIEWER | Daniel F. Kripke, M.D.  
|          | Professor of Psychiatry Emeritus 
|          | University of California, San Diego (USA) |
|          | The reviewer is a long-time critic of hypnotics who has recently proposed U.S. Food and Drug Administration action to mandate additional Phase IV safety trials or else to restrict hypnotic indications. See Sleep Medicine, 2016, http://dx.doi.org/10.1016/j.sleep.2015.12.011, the FDA documents at https://www.regulations.gov/#!docketDetail;D=FDA-2015-P-3959 and www.DarkSideOfSleepingPills.com. |

| REVIEW RETURNED | 24-Mar-2016 |

| GENERAL COMMENTS | This proposed study is a general inquiry into the beliefs, motivations and other factors leading to inpatient and outpatient prescription of hypnotics and benzodiazepines. Because of wide consensus that these drugs are dangerous and often over-utilized, further understanding will be important. With access to hospital and insurance records, the investigators have an opportunity to give a modern description of inpatient hypnotics prescribing that will be unique. They may also be able to examine correlates of hypnotics administration such as infections, depression, asthma, falls, prolonged hospital lengths-of-stay, and possible early readmissions, some of which have never been analyzed systematically. The exploratory protocol is quite nonspecific and lacking in methodologic details, yet it may make a valuable contribution to coping with the large and expensive prescribing problem that hypnotics present. Although the “Z” drugs are used predominantly for sleep, some benzodiazepines are traditionally used for sleep, some are traditionally used as daytime tranquillizers and sedatives, and some have been used for both purposes. Certain antidepressants (e.g., trazodone) and antipsychotics (e.g., quetiapine) are currently commonly used for sleep in the United States. How would distinctions be made as to whether the drug was prescribed for sleep or for another purpose? Would the analyses distinguish by purpose of prescription? |
Will chart review or secondary analysis of health insurance data attempt to document adverse correlates of hospital prescription of hypnotics that have been previously reported, such as falls, infections, and occurrences of confusion or dementia? Demonstration of such correlations (even with causality unproven) would be helpful in motivating patients and caregivers to forgo use of hypnotics and sedatives. Hospital length of stay and frequency of readmission are also important outcomes (especially to insurers), that have not been previously studied in relationship to in-hospital prescriptions of hypnotics and sedatives. Data from Taiwan and Great Britain also suggest that outpatient use of hypnotics is associated with increased hospital admissions for infections (e.g., pneumonia), asthma and suicide attempts, that might be analyzed through more complex undertakings.1-4

In the past, some occasional audits of hospital prescribing have noted that "prn" prescriptions were rarely associated with a diagnosed indication, such as insomnia, and such prescriptions were rarely otherwise explained in the medical records. This remains true to some extent in modern outpatient prescribing in the United States.5 Moreover, in some hospital settings, the physicians may have had little awareness of how much the "prn" hypnotics and sedatives that were ordered were actually administered. It would be valuable if information of this sort could be gathered.

In terms of interventions, the question is quite different for inpatient and outpatient care. It might be that physicians, nurses, and patients believe that hypnotics are effective in the hospital, and there were some placebo-controlled randomized trials several decades ago, but the reviewer knows of no clinical trials evidence of effectiveness with the current crop of hypnotics for inpatients. Specifically, the reviewer knows of no evidence that inpatient use of hypnotics improves overall hospitalization outcomes and patient health. The authors are asking a good question by inquiring why physicians and nurses administer these drugs. It might be that hypnotics produce some increase in sleep but also an increase in amnesia, confusion, and falls. In balance, is giving a hypnotic making the nurse’s and physician’s work easier or harder? For outpatients, the U.S. Agency for Healthcare Research and Quality recently issued a systematic review of outpatient treatment that found that cognitive-behavioral methods seemed to have better efficacy and much less risk than hypnotics,6 but the reviewer knows of no comparable applications of cognitive-behavioral methods in general hospital settings. A recent outpatient self-efficacy randomized trial was successful in Canada in reducing use of hypnotics,7 based on providing brief information about hypnotics to patients, but such methods may have never been tried in inpatients. This might be the most practical approach to pilot for a controlled trial.

Reference List

(2) Huang CY, Chou FH, Huang YS, Yang CJ, Su YC, Juang SY et al. The association between zolpidem and infection in patients with


REVIEWER
Malcolm lader
P056, Institute of Psychiatry, Psychology and Neuroscience, King's College London

REVIEW RETURNED
27-Mar-2016

GENERAL COMMENTS
I found it extremely difficult to assess this paper. It describes a protocol not a data paper. It presumably follows the successful application to the the fund-giving body. The study has been refereed and agreed.

Nevertheless, the study has, in my opinion, a major shortcoming. The protocol concentrates on the prescribing of sedatives and hypnotics at the interface between primary and secondary care. Yet it is unclear if enough is known about prescribing patterns in the primary and secondary areas at the research sites to warrant this focus on the interaction.

Leaving this aside as not susceptible to further modification at this stage, the question remains as to whether any purpose is served by publishing this protocol. Presumably it is on record somewhere as a registered protocol as it contains some elements of a clinical trial. That should suffice.

However, whether to publish is essentially a matter of editorial policy. I cannot see that it would be useful as the methodology is not innovative nor is it described in enough detail for the expert to replicate in due course. My advice is to reject.

VERSION 1 – AUTHOR RESPONSE
Reviewer 1
1. They may also be able to examine correlates of hypnotics administration such as infections,
depression, asthma, falls, prolonged hospital lengths-of-stay, and possible early readmissions, some of which have never been analyzed systematically.

Authors’ response

The data in the chart review is a cross-sectional analysis of anonymized patient records for the hospital episodes of older patients (65 and older) during a three-month time period. Most of the clinical data the Reviewer suggests to examine in detail are not part of the data extraction procedures. Therefore, it will not be possible to systematically analyze relationships between hypnotic use and infections or early readmissions. We thank the reviewer for the idea to study the relation between falls and the use of hypnotics. For this reason, we just sent an amendment to the ethics committee so that we can study this relation. However, even if the committee confirms the amendment, this will not be part of the current study so that we cannot include this idea in the study protocol. By the way, due to ‘confounding by indication’, any associations between falls and the drugs under study are limited in their validity as long as we cannot perform a RCT.

Since we have some data about the main diagnosis and other diagnoses, it may be possible to look for correlations with depression or asthma although this is not the main focus of our research question. Rather, we want to know the prevalence of benzodiazepine and Z-drug use in the hospital as well as whether these drugs were being taken before hospital admission and/or continued after discharge. Although the hypothesis that hypnotic use may prolong the hospital stay is very intriguing, the length of hospital stay is influenced by so many different factors that it would be impossible to determine the effect of hypnotics on length of stay using our study design and data source.

2. How would distinctions be made as to whether the drug was prescribed for sleep or for another purpose? Would the analyses distinguish by purpose of prescription?

Authors’ response

This is a very relevant point. Due to the nature of the hospital record data, we cannot distinguish the purpose for the hypnotic prescription (sleep or agitation, etc.). Due to the fact that sleeping problems are the most common reason for such prescriptions in the hospital setting, we maintain that our study design will give insight about this with the limitation that the treatment with hypnotics for other purposes cannot be analyzed separately. We have added this limitation to the manuscript on page 13, lines 24 ff.

3. Will chart review or secondary analysis of health insurance data attempt to document adverse correlates of hospital prescription of hypnotics that have been previously reported, such as falls, infections, and occurrences of confusion or dementia? Demonstration of such correlations (even with causality unproven) would be helpful in motivating patients and caregivers to forgo use of hypnotics and sedatives. Hospital length of stay and frequency of readmission are also important outcomes (especially to insurers), that have not been previously studied in relationship to in-hospital prescriptions of hypnotics and sedatives.

Authors’ response

We agree that it would be valuable to describe correlations between hypnotic use and adverse events. As mentioned in our comment #1 above, we are, to date, unable to analyze the records we have for adverse events (falls, confusion, infections) over time. Apart from the confounding effect, it would be necessary to follow patients (diagnoses, treatments, health service utilization) longitudinally across care sectors (ambulatory care, hospital care, nursing home care, rehabilitation, etc.). Such a single, longitudinal data source does not exist in Germany and the linking of multiple data sources is forbidden in Germany due to data protection laws.

4. In the past, some occasional audits of hospital prescribing have noted that “prn” prescriptions were rarely associated with a diagnosed indication, such as insomnia, and such prescriptions were rarely otherwise explained in the medical records. […] Moreover, in some hospital settings, the physicians may have had little awareness of how much the “prn” hypnotics and sedatives that were ordered were actually administered. It would be valuable if information of this sort could be gathered.
Authors' response
In the questionnaire for hospital doctors and nurses, we ask both professional groups how often benzodiazepines, Z-drugs, anti-depressants, neuroleptics, etc. are used on their floor as well as their perception of the most common benefits and risks associated with benzodiazepines and Z-drugs. If we find any differences between the professional groups, they will be discussed in focus groups and will probably become an important focus of the intervention. We have added this to the manuscript on page 8, line 22-25.

5. Specifically, the reviewer knows of no evidence that inpatient use of hypnotics improves overall hospitalization outcomes and patient health. The authors are asking a good question by inquiring why physicians and nurses administer these drugs. It might be that hypnotics produce some increase in sleep but also an increase in amnesia, confusion, and falls. In balance, is giving a hypnotic making the nurse's and physician's work easier or harder?

Authors' response
Thank you for sharing your ideas with us. In the fact, we have had similar thoughts about the short and long-term effects of hypnotic use. Particularly, we want to know whether factors like high workload, division of labor or lack of time are associated with an increased use of hypnotics and sedatives. However, these are sensitive issues so that we will not ask these questions in a standardized format but include them in the qualitative part of our study. They will be topics of our interview guide and will be addressed in the interviews only when our interview partners do not talk spontaneously about them. We have added this information on page 9, line 11 ff.

6. For outpatients, the U.S. Agency for Healthcare Research and Quality recently issued a systematic review of outpatient treatment that found that cognitive-behavioral methods seemed to have better efficacy and much less risk than hypnotics, but the reviewer knows of no comparable applications of cognitive-behavioral methods in general hospital settings. A recent outpatient self-efficacy randomized trial was successful in Canada in reducing use of hypnotics, based on providing brief information about hypnotics to patients, but such methods may have never been tried in inpatients. This might be the most practical approach to pilot for a controlled trial.

Authors' response
Thank you very much for mentioning this previous research. We are familiar with this cluster randomized trial [1]. A patient empowerment intervention – in the absence of initial physician involvement – seems to be an effective instrument to reduce the use of hypnotics and sedatives. Additionally, the fact raised by the authors that benzodiazepines were sometimes substituted with equally harmful sedative medication, is well-known to us as well. A systematic review showed, that cognitive behavioral therapy for the treatment of insomnia was effective in treating sleeping disorders [2]. If possible, we will consider these points as we work together with our partners in the local hospital and practices to develop effective interventions. However, our challenge will be to develop interventions which take into account the different attitudes and opinions of GPs as well as hospital doctors and nurses of the collaborating hospital. This seems to be the only way to change behavior and to influence the use of hypnotics and sedatives in a regional hospital as an exemplary case. We will consider the current state of research when developing effective interventions. This information has been added on page 10, lines 19-20.

Reviewer 2
7. The protocol concentrates on the prescribing of sedatives and hypnotics at the interface between primary and secondary care. Yet it is unclear if enough is known about prescribing patterns in the primary and secondary areas at the research sites to warrant this focus on the interaction.

Authors' response
There is a clear ‘yes’ to the reviewer’s question. First of all, we cite several studies in the first paragraph of the Introduction which report an alarming use of hypnotics and sedatives in hospitals. Then we cite some studies on GPs’ attitudes towards benzodiazepines and Z-drugs which show
some misconceptions about the benefits and risks of these drugs (see third para of the Introduction).
And we discuss the problem of “private prescriptions” in the fifth para of the Introduction—a special problem in Germany with private prescriptions making up nearly half of all prescriptions for zolpidem. And we know that there is an interface problem of discontinuation of drugs started before hospital admission and an even more severe problem with drugs started in the hospital and recommended for further use in primary care, sometimes without sufficient evidence (see end of second para of the Introduction). But we have only limited knowledge about the attitudes of hospital doctors and nurses towards these drugs and how they may affect their use. And so this will be the first focus of our study. And we know from anecdotal evidence that sleeping pills are a matter of concern between primary and secondary care, the second focus of our study. Last year, a further survey [3] was published that shows the dissatisfaction of GPs with the hospital prescribing policy in the case of sleeping pills. We include this reference in the new version (page 4, lines 15 ff.).

8. The methodology is not innovative nor is it described in enough detail for the expert to replicate in due course.
Authors’ response
An innovative aspect of our study is the close co-operation between a university department, a regional general hospital and the GPs in the surrounding area. We are not aware of a similar project in Germany, given its rather strict separation between academic medicine and primary and secondary care. This project opens the opportunity to investigate the attitudes and experiences of doctors and nurses concerning hypnotics and sedatives as a basis for a later intervention. Here again, both professional groups work rather isolated from each other and a project to support co-operation and interaction is innovative.
However, it is true that the description of our research process is not transparent enough. Therefore we decided to include the questionnaires and interview guides used in the study. The questionnaires are based on previous work of Hoffmann [4] (see reference 19). Hoffmann developed and translated the questionnaire on the basis of a similar survey from Sivertsen et al. [5] and Siriwardena (2006) [6]. In order to give other researchers more insight into the way we will perform the qualitative part of the study, we have added (translations of) the interview guides for GPs, hospital doctors and nurses. We now note this in the text on page 9, lines 22-23 and have added the guidelines to the manuscript in the Appendices 1-3.

References
Understanding and reducing the prescription of hypnotics and sedatives at the interface of hospital care and general practice: a protocol for a mixed-methods study

Stephanie Heinemann, Vivien Weiβ, Kati Straube, Roland Nau, Thomas Grimmsmann, Wolfgang Himmel and Eva Hummers-Pradier

BMJ Open 2016 6:
doi: 10.1136/bmjopen-2016-011908

Updated information and services can be found at:
http://bmjopen.bmj.com/content/6/8/e011908

These include:

References
This article cites 19 articles, 2 of which you can access for free at:
http://bmjopen.bmj.com/content/6/8/e011908#BIBL

Open Access
This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

- Epidemiology (2174)
- General practice / Family practice (673)
- Health services research (1520)
- Pharmacology and therapeutics (451)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/