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Generic Assessment of Side Effects: GASE

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1. Aim of GASE

Side effects are frequently underreported in clinical trials. Although the evaluation of new drugs through the FDA and other national and international institutions is based on multiple clinical trials, many side effects remain undetected and have to be included in the product labelling information months or years after approval of the drug (Ioannidis & Contopoulos-Ioannidis, 1998; Lasser et al., 2002). Only half of serious adverse drug events are detected and documented in the Physician's Desk Reference within 7 years of drug approval (Bennett et al., 2005; Lasser et al., 2002). Only one fifth of clinical trials reported side effects adequately (e.g., Papanikoleaou, Churchill, Wahlbeck, Ioannidis, & Project, 2004). Some clinical studies reported symptom base rates for patient groups which are substantially lower than prevalence rates for healthy controls, indicating a clear underreporting of potential side effects in these studies; this led to the conclusion that ascertainment strategies for side effect assessment need to be substantially improved (Avorn, 2005; Rief, Avorn, & Barsky, 2006). Unreliable and insufficiently valid side effect reports carry the potential for conflict of interests (Andersson & Kaldo-Sandstrom, 2004) and for patient and doctor misinformation, and can result in patient harm and delayed detection of serious adverse events. At present, most side effects are only detected if they occur early during treatment, if they are frequent, and if they were expected at trial planning (Vandenbroucke & Psaty, 2008). No recommended procedure exists for detecting unexpected side effects.

Side effects are often assessed using an open question about patients' symptoms since the last assessment, frequently combined with a subjective rating of whether the symptoms

might be drug-induced. The advantage of this method is the absence of suggestion, and the lack of limitation to single symptoms from a list. The major disadvantage is underreporting due to response styles or memory biases (Turk et al., 2006). Indeed, using these ascertainment strategies, it remains unclear whether patients report all symptoms they perceive, whether patient and/or study doctors/nurses attribute these symptoms correctly to the drug, and whether study personnel decide that they are serious enough to be written down. It has been shown that physicians' responses to patient reports of adverse drug events are frequently reluctant, and physicians tend to deny any connection between the patient's symptom report and drug intake (Golomb, McGraw, Evans, & Dimsdale, 2007). The authors conclude that patient reports can sometimes be more reliable than physicians' reports for the detection of side effects. For the majority of research questions, unsystematic general inquiry methods are highly inappropriate for assessing side effects, if no additional methods are used.

Another approach is the use of specific checklists of symptoms that could be related to the drug. These lists usually focus on the expected side effects, and disregard a broader screening for symptoms. Therefore, they are not suitable for detecting unexpected side effects, and they do not allow comparison of side effect profiles of different drugs. An inadequate selection of items is a serious problem of specific checklists of side effects (Rabkin, Markowitz, Ocepekvelikson, & Wager, 1992).

To improve side effect ascertainment, the data of spontaneous reports and drug-specific assessments have to be complemented with systematic screenings for unexpected symptoms. It has been shown that systematically assessing side effects leads to considerably higher sensitivity of the assessment (Guy, Wilson, Brooking, Manov, & Fjetland, 1986). In this paper we use the term "generic side effects" for a list of symptoms that are frequently-reported side effects in clinical trials using very different drugs. These generic side effects can be used to screen for unexpected symptoms at different body sites. Generic side effects can indicate serious outcomes and complications (Wysowski & Swartz, 2005), and generic side effects are also frequent reasons for patients' discontinuation of drug intake. Therefore, an adequate assessment of unexpected, generic side effects offers a useful tool to improve the detection of serious complications, but also to detect reasons for patients' drug discontinuation and reduced medication acceptance. A list assessing generic side effects can also be used to compare general side effect profiles

of different drugs, to detect nocebo effects (Barsky, Saintfort, Rogers, & Borus, 2002; Rief et al., in press), or to analyse patients' and study assistants' patterns of symptom reporting.

Patient reporting is a valuable source for the detection of drug-induced side effects (Foster, van der Molen, & de Jong, 2007; Golomb, McGraw, Evans, & Dimsdale, 2007). However, some clinical conditions require that symptom reporting be based on expert ratings. Therefore, parallel forms of side effect assessment strategies for both doctors and patients are helpful. Moreover, it is important to compare potential side effects reported during drug treatment with symptom reports before drug treatment started, to decide whether symptoms really developed during drug treatment or whether they are potentially misattributed to drugs even though they had other causes. Therefore, the ascertainment strategy should allow baseline assessments.

To date, only a few generic assessment methods exist. One is the Systematic Assessment for Treatment Emergent Events (SAFTEE), which was introduced mainly for use in psychopharmacology (Levine, Schooler, & Moynihan, 1983). SAFTEE is a structured interview and consists of a general and systematic inquiry, including 78 questions. Nevertheless, SAFTEE has been widely criticised for being too long and time consuming, and having serious validity and specificity problems (e.g., it is not clear whether reported symptoms are coincidental or caused by the drug). No baseline measures or normative data for SAFTEE exist. The instructions are criticized as being too complicated, especially for the clinicians who perform the interview (Rabkin, Markowitz, Ocepekvelikson, & Wager, 1992).

To summarize, there is an urgent need for a structured assessment tool to analyse potential side effects of drugs, and to screen for unexpected symptoms in most body sites. Therefore, a questionnaire that features the advantages of a systematic side effect assessment and concurrently overcomes the major problems of SAFTEE is required. With GASE, "Generic Assessment of Side Effects", we would like to present an instrument that meets these requirements. GASE allows generic, economical, and specific assessment of drug side effects and can be used in pharmacological, other clinical, and psychological research without the necessity of conducting face-to-face interviews. In upcoming articles,

we will report normative data, comparison data of different clinical groups, and reference data for drug groups.

2. Description of GASE

Patient version:

GASE consists of 36 items (symptom descriptions) organized by body parts. GASE collects information on “symptoms” experienced during the past week. These symptoms can be rated as “not present”, “mild”, “moderate,” or “severe.” After rating the presence and severity of a symptom the patient has to make a decision as to whether the symptom is related to current medication. This procedure allows differentiation between common symptoms the patient frequently experiences and new, potentially drug-related events. In addition to the 36 systematic items there is a possibility to openly list and rate the severity of further symptoms. This procedure allows assessment of unexpected or unusual side effects. GASE can be filled in by a patient without further support and takes 5 minutes on average to complete, which is an advantage in comparison to time-consuming assessment with SAFTEE.

Expert rating / Doctor’s version:

As an option for counter-checking patient-reported side effects, and for clinical conditions that require expert ratings, a parallel form was developed. The symptom list of this expert rating version is comparable to the patient version, with the same number of items, although sometimes using expert labels instead of everyday language.

3. Construction of GASE

GASE was constructed with the purpose of assessing side effects independently of the prescribed drug. Nevertheless, GASE can be extended by adding specific potential side effects if a specific question concerning a drug is investigated. The generic approach makes GASE suitable for many research questions concerning the comparison of different drugs and also personal tendencies to experience and report side effects of drugs.

Therefore, the Top 20 Adverse Events Reported for Drugs from 1969 through 2002 based on case counts in the Food and Drug Administration’s Adverse Event Reporting System Database, including reports from all countries, were included in the measure (Wysowski & Swartz, 2005). These adverse events were the most common among 10,000 separate

adverse events for approximately 6,000 different drugs. For the purpose of patient-friendly assessment, more common descriptions of symptoms were sometimes chosen or, for the purpose of keeping the questionnaire short and generic, some symptoms were summed up into one category. Additionally, based on expert ratings (Dr. Rief, Dr. Glombiewski, Dr. Nestoriuc, Dr. Barsky), the most common adverse events included in SAFTEE but not listed within the FDA Top 20 Adverse Events were included in GASE (e.g., depressed mood, agitation), as well as the three most common pain symptoms (back pain, muscle pains, and joint pain instead of “pain” as listed by FDA). The exact source of each item is included in the attached version of GASE.

4. How to analyse GASE results?

We suggest using GASE not only during clinical trials, but also for baseline assessments. This makes the results more reliable and easier to interpret, although for some questions it might be acceptable to use only assessment points during or after treatment, and to compare the results with other representative data, or with other comparison groups. All items should be analysed on an item level (e.g., comparing frequency of this item with frequency at baseline). Moreover, patients’ or doctors’ attribution of symptoms as being “drug-induced” helps to analyse causality attributions. However, we also suggest computing total scores:

Composite Indices:

Symptom count: Sum of items with answers ≥ 1

Total Score: Sum of all item answers

Medication-attributed symptom count: Sum of confirmed items which are medication-attributed.

Total Score: Sum of all item answers of symptoms that are medication-attributed.

5. Outlook on the further development of GASE

To address further critical points concerning the assessment of drug side effects (Rabkin, Markowitz, Ocepekwelikson, & Wager, 1992), we included GASE in a representative national survey. The results will provide necessary base rates for symptoms assessed with GASE and information about attribution of these symptoms to drugs in the common German population. Additionally, we plan several measurements of validity and reliability

of GASE including a large sample of breast cancer patients and further samples of chronic pain patients.

Please note:

Please be aware that we will add references reporting normative data for age and sex groups, reference scores for drug groups, etc. For further details please contact the first author (rief@staff.uni-marburg.de).

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