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# Typology of drug discontinuation trials - Methodological recommendations

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## Abstract

**Objective:** Due to the increasing concerns about polypharmacy, there is a growing need for clinical recommendations for drug discontinuation. This requires studies investigating the process on several levels. This paper addresses the methodological problems of drug discontinuation trials (DDTs). To that end, we offer a new typology of research aims and corresponding methodological recommendations for trials evaluating drug discontinuation.

**Study Design and Setting:** Multi-stage development process, including literature search and expert panels.

**Results:** Clinical trials are only required in cases of scientific uncertainty. We identified three situations of uncertainty associated with drug discontinuation from which we derived three study types: 1) Uncertainty regarding the effectiveness and/or safety of a drug; 2) Uncertainty regarding the procedure of discontinuing a previously taken drug; 3) Uncertainty regarding the effectiveness of complex strategies used to discontinue one or more drugs. We developed specific methodological recommendations for each study type.

**Conclusion:** We offer a comprehensive definition of research aims, study designs, and methodological recommendations regarding DDTs. The typology we propose can help investigators clarify their research aims and study design. The type-specific methodological recommendation should improve the quality of future drug discontinuation trials. 

*Keywords:* Desprescribing; Drug discontinuation

## 1. Introduction

Polypharmacy is a major health risk. Medication use has steadily increased over the last two decades, particularly among older people. [1,2]. While this is the result of more and better treatment options, especially for chronic diseases, polypharmacy is also associated with several adverse outcomes. The regular intake of five or more medications is associated with an increased risk for higher mortality, falls and hospitalization, as well as adverse drug reactions and drug-drug interactions [3,4]. Furthermore, polypharmacy is a financial burden to individuals and health care systems [3,4].

Stopping medication, however, can be difficult. In recent decades, few research groups (among them, the Bruyère Deprescribing Guidelines Research Team (Canada); Primary Health Tasmania (Australia), etc.) have published several medication-specific recommendations (e.g., withdrawal of antihypertensives, antipsychotics, benzodiazepines, opioids, proton pump inhibitors, etc.) [5,6]. In addition, several generic discontinuation strategies were developed based on targeted questions to elicit appropriateness of drugs, like the Medication Appropriateness Index (MAI), [7]. However, the evidence for deprescribing

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medication is sparse in contrast to evidence provided by classical clinical trials investigating efficacy of treatment.

A closer look at trials evaluating drug discontinuation reveals several limitations. The number of published studies is small, and many suffer from methodological flaws. A systematic review by Grede and Thio et al. found inappropriate study designs, such as lack of control group, too small sample size, and insufficient follow up periods [8,9].

A more thorough methodological approach to drug discontinuation studies is needed. Only a few research groups are contributing to the evidence: Thompson et al. published a collection of articles addressing issues relevant to future investigations of deprescribing [10]. The authors formulated six priority areas: “1) Conducting high-quality and long-term clinical trials that measure patient-important outcomes, 2) Focusing on patient involvement and perspectives, 3) Investigating the pharmacoeconomics of deprescribing interventions, 4) Understanding deprescribing interventions in different populations, 5) Generating evidence on clinical management during deprescribing (e.g., managing adverse drug withdrawal effects, and subsequent re-prescribing), and 6) Implementing interventions in clinical practice.” [10]. Linsky et al. published a "deprescribing conceptual framework", which separates the decision to deprescribe from the process of implementation [11]. They thereby emphasize the complex interaction between patients, prescribers, and system influences [11]. In addition, Blom et al. addressed unique features relevant to the reporting of deprescribing trials [12]. The results were published as an elaboration of the CONSORT statement [12].

The work listed above is an important prelude to the scientific debate on research designs for evaluating drug discontinuation, which we would like to expand upon through this project. We believe a first step should be to clarify the objectives of a particular drug discontinuation trial (DDT). As a next step, details of study design and implementation should be outlined. Here we propose a new typology of research aims and offer methodological recommendations for trial designs evaluating drug discontinuation.

## 2. Methods

We established the working group “Methodology of DDTs” at the Department for General Practice at the Philipps-Universität Marburg, Germany. As a first step, we conducted a systematic review of published DDTs (funded by the German Federal Ministry of Education and Research) [8]. As expected, we found a wide range of clinical topics and study designs. The results also showed a substantial heterogeneity of motivations for conducting discontinuation studies, such as doubts concerning effectiveness and/or safety of drugs, proof of efficacy via discontinuation, or changes in therapy regimes. In a large proportion of cases, study designs were incongruent with study objectives; e.g., therapy was evaluated with observational design [8]. The large number of methodologically inadequate drug discontinuation studies motivated us to reflect upon and discuss possible improvements to the evidence base of this important clinical topic.

We therefore employed the following multi-stage development process:

### 2.1. Phase I – Type identification

The working group consisted of the authors AV, NG, JH, AB, and NDB. We collected clinical scenarios in which the question of deprescribing drugs typically arises. These scenarios were derived from relevant literature and clinician members’ own experience as primary care physicians. Based on typical clinical drug discontinuation scenarios, the team suggested the first draft of a typology for DDTs.

### 2.2. Phase II – Expert panel

The members of the expert panel were the authors IG, AS, UJW, AM, HS, as well as our aforementioned working group members. The participants are experts in the field of multimorbidity, polypharmacy, drug trials, and drug discontinuation. All expert panel members received the first version of the typology before a one day conference. They were asked to provide critical comments. These comments were made available to members during the meeting and discussed in the group. Afterwards, disagreement in the comments was reviewed by the working group.

### 2.3. Phase III - Development of the type-specific methodological recommendation

The types and the ideas of methodological recommendations further developed in the panel were presented at the Institute of Medical Biometry and Epidemiology (University of Hamburg, Germany). The methodological recommendations were revised in collaboration with the working group of Prof. Wegscheider (expert for clinical studies).

### 2.4. Phase IV - Second voting expert panel + last revision

After further revisions of the typology and type-specific methodological recommendations, we again requested the expert panel’s opinions and comments. All members of the expert panel were asked to submit written comments. Our working group then developed the final version, presented in this article. It was reviewed and unanimously endorsed by all authors.

## 3. Results

The multi-stage development process mentioned above led to the following typology of research aims and resulting methodological recommendations for DDTs.

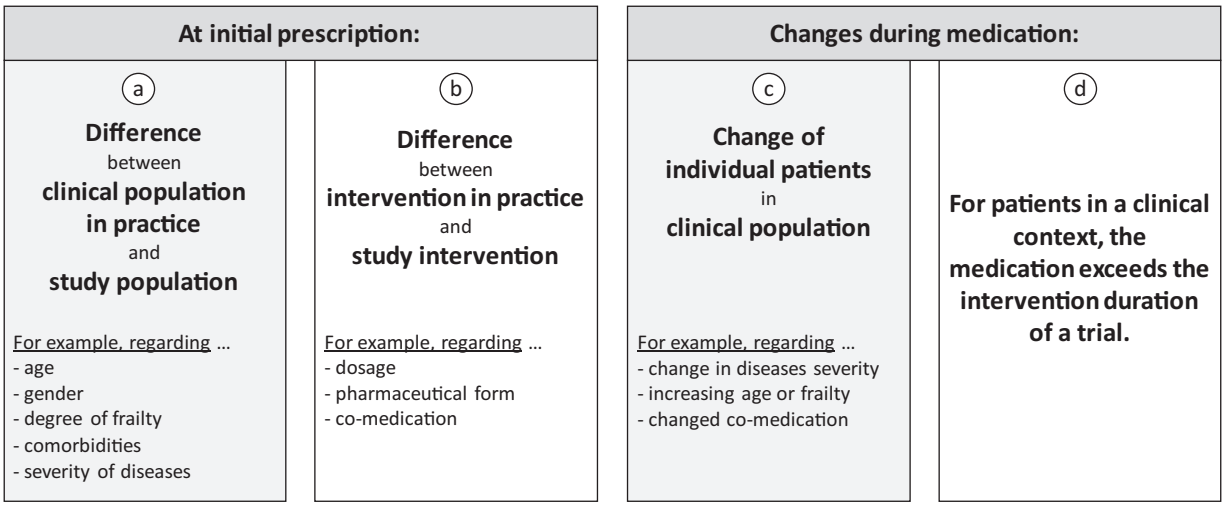


**Fig. 1.** Clinical scenarios which lead to doubts on effectiveness and/or safety of long-term medication (Type 1)

### *3.1. Definition 'Drug discontinuation trial'*

We define DDTs as studies which aim to evaluate the discontinuation of one or more drugs that were prescribed to patients in a clinical context.

### *3.2. Typology of research aims for evaluating drug discontinuation*

Clinical trials are only justified if uncertainty exists. We identified three types of uncertainty that are associated with drug discontinuation: Type 1) Uncertainty regarding the effectiveness and/or safety of a drug; Type 2) Uncertainty regarding the process of discontinuing a previously taken drug; Type 3) Uncertainty regarding the effectiveness of complex strategies used to discontinue one or more drugs.

#### *3.2.1. Type 1 – Doubts on effectiveness and/or safety*

Research question: Can drug X be discontinued without harm compared to the continuation of medication? The motivation for this research question stems from doubts about the efficacy and/or safety of a continuing drug therapy.

Clinical trials never fully reflect the situations clinicians are confronted with in their daily practice. Participants in clinical trials can differ from patients in a clinical context in numerous ways, for example, with regard to the severity of the target disease, demographic characteristics, comorbidities, comedications, or general health state. In order to let their patients benefit from evidence-based treatments, clinicians, and also guideline authors, extrapolate from the results of published studies to their individual patients, even in the face of considerable discrepancies.

Several scenarios are conceivable in which doubts arise as to whether extrapolation from studies to clinical populations can still be justified (Fig. 1).

(a) A difference between the clinical population in practice and the study population that already exists at the time of the first prescription. Possible reasons are, for example, age, gender, degree of frailty, comorbidities, or severity of diseases.
(b) A difference between the intervention in practice and the study intervention that already exists at the time of the first prescription. These differences can refer to, for example, dosage, pharmaceutical form, or co-medication.
(c) Patients in the clinical population undergoing changes during medication. These differences can relate to, for example, disease severity, diagnostic tests becoming more sensitive, increasing age or frailty, or changes in co-medication.
(d) Patients are prescribed medication for much longer periods than follow-up in clinical trials.

These doubts refer to the effectiveness and/or safety of long-term medication. Several scenarios may occur simultaneously. In these cases, a Type 1 DDT can be indicated. Table 1 illustrates examples of clinical scenarios from already published discontinuation trials.

#### *3.2.2. Type 2 – Discontinuation procedure*

Research question: How can drug X be discontinued without rebound and/or withdrawal reactions? The clinical starting point for this question is uncertainty regarding the discontinuation procedure. We define the discontinuation procedure as the practical steps required to terminate a particular long-term medication. In this setting, rebound or

**Table 1.** Examples for type-specific research questions

| Type | Clinical scenario | Research Question | Intervention | References |
|---|---|---|---|---|
| **Doubts on effectiveness and/or safety** | "… patients with rheumatoid arthritis … using adalimumab or etanercept … with stable low disease activity …" "…Treatment with TNF inhibitors is not without its drawbacks: they are associated with adverse effects … [and] treatment is costly…" | "To evaluate whether a disease activity guided strategy of dose reduction of two tumour necrosis factor (TNF) inhibitors, adalimumab or etanercept, is non-inferior in maintaining disease control in patients with rheumatoid arthritis compared with usual care." | "Disease activity guided dose reduction (advice to stepwise increase the injection interval every three months, until flare of disease activity or discontinuation) or usual care (no dose reduction advice)." | van Herwaarden N., et al. Disease activity guided dose reduction and withdrawal of adalimumab or etanercept compared with usual care in rheumatoid arthritis: open label, randomised controlled, non-inferiority trial. BMJ. 2015 Apr 9;350:h1389. doi: 10.1136/bmj.h1389. [1] |
| **Discontinuation procedure** | "Antiepileptic drug withdrawal may be an option for patients who have been seizure free for some years. The best withdrawal rate is questionable…" | "We aim to establish if a slow or a rapid withdrawal schedule of antiepileptic monotherapy influences relapse rate in adult patients with focal or generalized epilepsy who have been seizure free for at least 2 years." | "Patients will be randomized to a slow (160 days) or a rapid (60 days) schedule." | Gasparini S., et al. Rapid versus slow withdrawal of antiepileptic monotherapy in 2-year seizure-free adult patients with epilepsy (RASLOW) study: a pragmatic multicentre, prospective, randomized, controlled study. Neurol Sci. 2016 Apr; 37(4):579-83. doi: 10.1007/s10072-016-2483-3. Epub 2016 Jan 25. [2] |
| **Complex discontinuation strategy** | "Residents with a life expectancy greater than 4 weeks who consented to treatment with medication." | "To examine successful discontinuation of inappropriate medication use and to improve prescribing in nursing home residents." | "Multidisciplinary Multistep Medication Review (3MR) consisting of an assessment of the patient perspective, medical history, critical appraisal of medications, a meeting between the treating elder care physician and the pharmacist, and implementation of medication changes." | Wouters H., et al. Discontinuing Inappropriate Medication Use in Nursing Home Residents: A Cluster Randomized Controlled Trial. Ann Intern Med. 2017 Nov 7;167(9):609-617. doi: 10.7326/M16-2729. Epub 2017 Oct 10. [3] |

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[3] Wouters H, Scheper J, Koning H, Brouwer C, Twisk JW, van der Meer H et al. Discontinuing Inappropriate Medication Use in Nursing Home Residents: A Cluster Randomized Controlled Trial. Ann Intern Med 2017;167(9):609–17. https://doi.org/10.7326/M16-2729

withdrawal reactions are frequent. The procedure tries to minimize the physiological reactions of drug elimination.

'Withdrawal syndromes' are medication-specific acute symptoms which typically appear immediately after discontinuation and may resemble symptoms of the underlying disease; they are usually transient [13]. The term rebound describes an intensified recurrence of the same symptoms which had originally motivated treatment. This effect is based on counter-regulatory mechanisms activated by treatment and excessive counter-regulation after stopping the medication [13]. Typical examples are worsening reflux symptoms after stopping proton pump inhibitors, or palpitation and rise in blood pressure after cessation of beta blockers. Management of withdrawal syndromes and rebound typically includes schemes of down tapering and the use of rescue medication.

Investigators conducting Type 2 studies should start with the assumption that the discontinuation of a certain drug is desirable. Research should focus on finding the optimal way to achieve this for the individual patient.

### *3.2.3. Type 3 – Complex discontinuation strategy*

Research question: Does a complex discontinuation strategy effectively reduce the intake of one or more drugs?

We define a discontinuation strategy as a complex intervention to help clinicians and patients discontinue a long-term medication that is no longer considered beneficial. It typically consists of information, advice, motivation, and emotional support. During this process, health care providers have to take the following steps: (1) provide the patient with information on the benefits and/or risks of long-term medications; (2) explore the patient's motivation for medication and possible discontinuation; (3) address associated fears, clarify preferences and goals that the patient consider relevant; (4) if there are several candidate drugs, discuss priorities; (5) propose practical steps including dose reduction, timing, use of rescue medication, follow-up visits, and help in case of emergencies [14–16]. Once a decision has been made, it must be documented. A written plan should be handed to the patient covering the issues mentioned above. Like in other attempts to change health-related behaviors, such as smoking cessation or change in diet, the challenge is approached with a realistic attitude [17,18]. Providers must be aware that such interventions are only successful in a minority of cases [19].

A well-known example for a complex discontinuation strategy is the Geriatric-Palliative Approach for Improving Drug Therapy by Garfinkel et al. [20]. To evaluate this strategy, the authors compared the algorithm in the intervention group with a usual care control group. Outcome variables were death rate, referrals to hospital, and costs in conjunction with change in medications [20]. For further examples, see Table 1. Another example for these types of studies are trials that evaluated strategies for helping patients stop taking benzodiazepines.

### 3.3. Obsolete treatments

Obsolete treatments may present Type 2 and Type 3 uncertainties. Thyroid hormones prescribed for years or even decades provide an extreme example. Diagnosis of relevant thyroid disease often dates back many years, the original documentation is often lost, and doctors re-prescribe the medication with the assumption that there has been some justification in the past. Attempts to stop the drug often meet patients' resistance [21]. In order to gain evidence for this dilemma, a DDT trial investigating discontinuation procedures and evaluating complex strategies would be helpful.

### 3.4. Methodological recommendations for discontinuation trials

Current frameworks for the design and conduct of clinical trials have been developed with the introduction and evaluation of new treatments in mind. Most requirements to avoid bias also apply to discontinuation trials. The expert panel, however, made the following additional recommendations specific to drug discontinuation (Table 2).

#### 3.4.1. Research aim

Independent of the type-specific focus (effectiveness and/or safety vs. discontinuation procedure vs. complex discontinuation strategy), the research questions should address efficacy and safety (discontinuation without harm). Further information about formulation of hypothesis (superiority vs. non-inferiority) is described in the section 3.4.7 Outcomes.

#### 3.4.2. Study design

In order to address confounders, the research questions from all study types should be investigated within a randomized controlled design. Type 3 studies typically require a cluster randomization because health care providers conducting the complex study intervention cannot be expected to switch between intervention and control procedure. Randomization at the health care unit level, such as practice, hospital ward, etc., is thus indicated.

#### 3.4.3. Study population

DDTs include patients who have been prescribed a certain medication as part of their routine treatment. It is often assumed that the long-term medication under consideration was prescribed without a planned withdrawal date. This applies, for example, to antihypertensive or lipid-lowering drugs. Oral anticoagulation after deep vein thrombosis provides a different case, as this treatment is usually only prescribed for a limited time span.

#### 3.4.4. Intervention-/ Control group

In Type 1 studies, medication is discontinued in the intervention group; in the control group, medication is taken as before. Type 2 and 3 studies aim to test the new discontinuation procedure or strategy in the intervention group. In the control group, an established procedure or strategy should be conducted. The definition of cut-offs for safety indications and rescue measures can be indicated in Type 1, 2, and 3 studies. Type 3 studies require the development and exploratory testing of a complex intervention, which usually includes training health care providers, information materials for patients, specific documentation, reminders for health care teams, procedures for feedback, and audit. See the British Medical Research Council Guidance [22].

#### 3.4.5. Randomization

Type 1 and 2 studies are typically randomized at the patient level. In Type 3 studies, on the other hand, randomization is usually carried out at the level of the working units of the health care providers who carry out the intervention.

#### 3.4.6. Blinding

Blinding patients and study and clinical personnel to treatment allocation reduces observation bias and ensures adherence. Whether blinding is appropriate in a drug discontinuation study depends on the research objectives of

**Table 2.** Type-specific methodological considerations

| | | Type 1 Doubts on effectiveness and/or safety | Type 2 Discontinuation procedure [I] | Type 3 Complex discontinuation strategy [II] |
|---|---|---|---|---|
| Study population | | Patients with a long-term medication. | Patients with a long-term medication. The decision for discontinuation has already been made. | Patients with a long-term medication; typically nested at healthcare units. |
| Research question | | Can drug X be discontinued without harm compared to the continuation of medication? | How can drug X be discontinued without rebound and/or withdrawal reactions? | Does a complex discontinuation strategy effectively reduce the intake of one or more drug(s)? |
| Study design: RCT | Intervention group | Medication will be discontinued | Discontinuation procedure (which should be evaluated) | Discontinuation strategy (which should be evaluated) |
| | Control group | Medication will be taken as before | Discontinuation procedure (established procedure, e.g. usual care) | Discontinuation strategy (established strategy, e.g. usual care) |
| Randomization | | Yes (Randomization at patient level) | Yes (Randomization at patient level) | Yes (Cluster randomization at the level of the working units of the health care providers who carry out the intervention). Randomization after patient recruitment. |
| Blinding | | Double-blinding of providers and patients. Placebo in the intervention group is indicated. | Double-blinding of providers and patients. | In case of provider behavior-based interventions, blinding is often not possible or explicitly not required. |
| Follow-up | | Follow-up time depends on the outcomes. Regular clinical monitoring to ensure patient safety. | | |
| Outcome | Primary | Co-primary endpoint consisting of a clinical safety endpoint (non-inferiority hypothesis) and the discontinuation rate as an efficacy parameter (superiority hypothesis). | | |
| | Secondary | Further clinical efficacy and safety endpoint, economic outcomes, etc. | | |
| Analysis | | Intention-to-treat analysis + Per-protocol analysis | | |

I Discontinuation procedures include practical steps required to terminate a particular long-term medication at patient level (aim: avoidance of withdrawal or rebound phenomena)

II Discontinuation strategy implies a complex intervention for helping doctors go through the process of discontinuing a long-term medication.

the trial. For a Type 1 study evaluating the effect of a drug on disease episodes, such as exacerbations of COPD or cardiovascular events, blinding with an identical placebo in the discontinuation arm is appropriate. Investigators can thus obtain an estimate of the biological effect of the drug. Cognitive or emotional reactions to the (non-) treatment can thus be eliminated. In Type 3 trials, however, these reactions are the very focus of the study. Dealing with the patient's subjective experience to discontinuation and her psychological and physiological reactions, is an important task for clinicians. In our view, in Type 3 studies blinding generally does not match the research objectives. For Type 2 studies the choice of comparator and possible blinding depends on the focus of study (physiological versus psychological).

### *3.4.7. Outcomes*

For all types of discontinuation trials, we recommend two co-primary endpoints: clinical safety, and discontinuation rate as marker for efficacy. The clinical safety endpoint should be clinically relevant and related to the initial medical condition, such as pain intensity reported by patients undergoing discontinuation of analgesics. Monitoring TSH and fT4 when stopping thyroid hormone would be another example. The clinical safety endpoint should be evaluated by a non-inferiority hypothesis implying that drug discontinuation can be undertaken without the disease worsening. As an efficacy outcome, in most instances the proportion of patients in whom discontinuation has been successful is appropriate. The endpoint 'discontinuation rate' should be evaluated by a superiority hypothesis.

For safety reasons, drug discontinuation should be carefully monitored (e.g., by patient interviews, clinical examinations, biomarker test, and medical imaging). Not achieving discontinuation can be associated with several mechanisms: deterioration of the disease, unmanageable withdrawal symptoms, a psychological reaction by the patient, or interference by other health care providers, e.g., after hospital admission. For a clinical recommendation to be justified, both the safety and the efficacy evaluations must be successfully completed.

*3.4.8. Follow-up*

The duration of the follow-up depends on the condition, the study drug, and the outcomes of interest. Symptom-based measures, such as pain intensity after discontinuing an analgesic, require only a short follow-up period. For drugs prescribed to prevent future disease events, such as vascular disease or exacerbations of COPD, more than 12 months are often required.

*3.4.9. Analysis*

With respect to the co-primary endpoints mentioned above, we recommend both per per-protocol (PP) and intent-to-treat analysis (ITT). The implementation of both procedures is based on the use of the co-primary endpoint. For the efficacy endpoint, usually part of a superiority hypothesis, an ITT analysis is preferable [23]. For the non-inferiority hypothesis referring to the co-primary safety outcome, an additional PP analysis is justified [23]. All other statistical requirements for planning a DDT, like sample size calculation or the selection of statistical tests, are concordant with established standards.

*3.4.10. Ethical considerations*

In order to ensure study patients' safety, the evidence available prior to the study must be carefully reviewed. As a useful analogy, researchers should have research programs in mind needed for the evaluation of novel treatments. Extensive animal as well as phase 1 and 2 studies in humans are conducted before the main efficacy and safety hypotheses are evaluated in phase 3 trials. Although this kind of evidence will neither be available nor relevant to the issue of deprescribing, the success of a discontinuation study must be sufficiently likely to justify the inclusion and randomization of patients. In studies investigating drugs preventing future disease episodes, an interim safety analysis can be appropriate.

## 4. Discussion

We propose a typology of DDTs addressing research objectives and study designs. The three types are derived from clinical discontinuation situations, which are typically associated with uncertainty: 1) Uncertainty regarding the effectiveness and/or safety of a drug; 2) Uncertainty regarding the procedure of discontinuing a previously taken drug; 3) Uncertainty regarding the effectiveness of complex strategies used to discontinue one or more drugs. Additionally, we developed specific methodological recommendations for each study type.

The need for a more differentiated view on the research questions of drug discontinuation has already been described elsewhere [10,24]. Reeve et al. describe two groups of deprescribing studies: 1) "Studies focusing on whether an intervention (e.g., educational intervention, medication review) is effective"; 2) "Study targets a specific medication…where use of this medication is considered inappropriate" [24]. These two groups seem to be similar to Type 3 (complex discontinuation strategy) and Type 1 (doubts on effectiveness and/or safety) of our typology, respectively. However, we think that our Type 2 (discontinuation procedure) is an important addition to the framework. Evidence for the discontinuation procedures is currently lacking, especially in cases of medication with a high risk of dependency, such as benzodiazepines, opiates, or those with a high risk of rebound, such as antidepressants or proton pump inhibitors.

Clinicians planning a drug discontinuation study often require information which should ideally be obtained from other types of DDTs. For example, when planning a Type 3 study, knowledge regarding discontinuation procedures is useful. This knowledge may be derived from formal studies, but sometimes only clinical experience is available.

Do DDTs represent a particular study design entity? The suggestions regarding research aims, study population, and outcomes of DDTs made above support this consideration. On the other hand, the philosophy underlying discontinuation studies and most design features are identical to established clinical trials. For this reason, we do not postulate an own design entity for drug discontinuations trials, but suggest that certain aspects be taken into account when designing a discontinuation study. We hope to motivate investigators to undertake DDT studies and improve the quality of future studies in this area.

In their narrative review, Gnjidic et al. discuss the methodology of previously published DDT studies [25]. They found that clinical endpoints as well as discontinuation rates are used as outcomes in DDT studies [25]. In their recommendations for DDT studies, the Bruyère Deprescribing Guidelines Research Team also formulate that both clinical endpoints and discontinuation rates can be used as outcomes [5]. We conclude that both are relevant and should be evaluated concurrently as co-primary outcomes; the discontinuation rate represents the focus of DDTs, and the clinical endpoint highlights safety aspects. Blom et al. developed recommendations for reporting DDTs extending the CONSORT statement [12]. Our work complements their proposal with a typology of research questions and recommendations for type-specific methods.

### 4.1. Implication for the future

Compared to classical clinical trials evaluating novel treatments, deprescribing studies are a recent addition to the world of clinical research. Study designs, choice of comparisons, outcomes, methods of analysis, to name but a few, are still in a state of flux. Before making these choices, however, investigators must define their research objectives. Different objectives imply different, sometimes even opposing, methodological consequences. We hope that our typology will help researchers make this important first step as they prepare studies investigating drug discontinuation.

## CRediT authorship contribution statement

**Annika Viniol:** Conceptualization, Project administration, Supervision, Writing - original draft, Writing - review & editing. **Jörg Haasenritter:** Writing - review & editing. **Nina Grede:** Conceptualization, Writing - review & editing. **Karl Wegscheider:** Conceptualization, Writing - review & editing. **Annette Becker:** Conceptualization, Writing - review & editing. **Helmut Sitter:** Conceptualization, Writing - review & editing. **Ildikó Gágyor:** Conceptualization, Writing - review & editing. **Andreas Sönnichsen:** Conceptualization, Writing - review & editing. **Achim Mortsiefer:** Conceptualization, Writing - review & editing. **Ulrike Junius-Walker:** Conceptualization, Writing - review & editing. **Norbert Donner-Banzhoff:** Conceptualization, Supervision, Writing - original draft, Writing - review & editing.

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