European Addiction Research

Commentary

Eur Addict Res 2022;28:231–239
DOI: 10.1159/000521996

Received: April 14, 2021
Accepted: January 14, 2022
Published online: February 23, 2022

Monitoring Opioids in Europe: The Need for Shared Definitions and Measuring Drivers of Opioid Use and Related Harms

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Keywords
Prescription opioids · Illegal opioids · Opioid dependence · Europe

Abstract
The past 20 years, the USA is facing a serious opioid crisis initiated by an increase in prescription opioid use. Europe has also seen an increase in prescription opioid use, but the extent of related harm is still largely unknown. Given the impact of the US opioid epidemic, it is important to closely monitor signs of emerging opioid-related problems to guarantee early warnings and timely actions. Shared and meaningful definitions for opioid use and related harms, and relevant information about specific drivers for opioid use and related problems are needed for an adequate policy response. In this commentary, we discuss these definitions, the need to know more about the specific drivers for increased opioid use, its related harm, and proposals for strategies to move forward. Policy recommendations include making a distinction between licit and illicit opioids when monitoring and reporting on opioid-related harm, and using oral morphine equivalents to quantify prescription opioid use in a clinically relevant and comparable manner. A major topic of further research is exploring unique and universal drivers of prescription opioid (mis)use across Europe, in particular the role of opioid diversion.

Introduction

For the past 20 years, the USA has been facing a serious opioid crisis. The number of opioid-related deaths increased from 3.0 per 100,000 in 2000 [1] to 14.9 per 100,000 in 2017 and levelled off to 14.6 per 100,000 in 2018 [2]. Between 1999 and 2018, a total of 446,032 deaths involved opioids [2]. The opioid epidemic was initially

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driven by an increase in medical (prescription) opioid use, as a result of, amongst other things, the inclusion of pain as the fifth vital sign and the incorrect belief that opioid addiction is rare in prescription opioid users [3]. While the opioid crisis in the USA started with increased prescription opioid use and abuse, many prescription opioid users later switched to heroin because of the lower cost and higher availability [4]. This change was subsequently paralleled by an increase in heroin overdose deaths around 2010. Since 2013/14, fentanyl has become the main cause of opioid-related overdose deaths in North America, most likely due to adulteration of heroin with illicitly manufactured fentanyl (IMF) [5].

Europe has also seen a steady increase in prescription opioid use over the past 10 years, mainly due to increased tramadol, fentanyl, and oxycodone prescribing [6]. Several reports have raised concerns about this increase in prescription opioid use and the potentially associated opioid-related harms, including opioid-related deaths [7–9]. However, the level of prescription opioid use [10] and opioid-related deaths in most European countries is still (much) lower than in the USA. For example, opioid-related mortality in the EU was 1.3 per 100,000 population in 2017 (US: 14.9 per 100,000) [11]. Although opioid-related harm appears limited in the EU as a whole, there are some EU (constituent) countries (e.g., Estonia and Scotland) that reported an opioid-related mortality rate similar to the USA [6]. A recent investigation into prescription opioid use and related harms in 19 European countries found that only Scotland was facing an opioid epidemic comparable in severity to the USA, with an opioid-related mortality of 22.7 per 100,000 in 2018 [11]. However, the authors noted that comparison of opioid-related harm (e.g., hospital admissions, treatment demand, and mortality) between countries was limited by differences in definitions. In a recent systematic review published in European Addiction Research, van Amsterdam et al. [12] investigated the drivers for the high opioid-related death rate in Scotland and compared them to England/Wales. Important drivers contributing to the opioid-related mortality in Scotland were: (1) a high number of drug users, (2) steep ageing of drug users, (3) polydrug use (e.g., benzodiazepines and gabapentinoids), and (4) low-treatment coverage for opioid addiction. In addition, they noted that restricting opioid prescribing would be an important step in reducing opioid-related mortality in Scotland.

Given the impact of the opioid epidemic in the USA and Scotland, and the increased use of prescription opioids in Europe, it is important to closely monitor the situation in Europe for signs of emerging opioid-related problems and respond adequately and timely to such signals. To implement a balanced policy response at a national or regional level, the availability of reliable epidemiological data on opioid use and opioid-related harm is key. This commentary elaborates on several issues that should be considered when analysing the current opioid situation in Europe.

Although the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is regularly reporting about the opioid situation in the EU, these reports suffer from serious limitations due to the inconsistent use of definitions per reporting country and a lack of information on potential drivers per country [13]. In addition, the EMCDDA is mostly concerned with harm related to illegal opioids, whereas data on harm specifically related to prescription opioids is lacking. We argue that improved reporting requires: (1) clear and shared definitions of different patterns of opioid use and opioid-related harm, and (2) better knowledge of the multiple drivers of prescription and illicit opioid use, and related harms in each country or regions within countries (e.g., Scotland vs. England [14]).

Definition

The use of shared definitions is vital when reporting and comparing results on opioid use and related harms between countries and changes over time. Here, we discuss definition issues for: (1a) types of opioids (prescription vs. illicit opioids), (1b) quantification of opioid doses, (1c) patterns of opioid use (Table 1), and (1d) opioid-related mortality.

Prescription and Illicit Opioids

The distinction between prescription opioids and illicit opioids is often not as clear as one would hope, despite seemingly clear definitions. Prescription opioids are manufactured legally by pharmaceutical companies and are mostly obtained through bona fide medical prescriptions. In contrast, illicit opioids are manufactured and distributed by illicit means and are generally used for non-medical (e.g., recreational use, addiction) purposes. However, prescription opioids can be used legally as prescribed, legally not-as-prescribed (e.g., too frequent, too long, too much, other route of administration), but also diverted to the illegal market and then used illicitly.

A clear distinction between prescription and illicit opioids is not always possible. For example, fentanyl is currently manufactured by both legal and illegal producers, however toxicological screenings cannot distinguish be-

Table 1. Overview of definitions for different types of opioids, units for quantifying dose, and use patterns relevant for research

Definition	Description
Types of opioids	
Prescription opioid	Opioid manufactured legally by pharmaceutical companies and mostly obtained through legal medical prescriptions
Illicit opioid	Opioid manufactured and distributed by illicit means and generally used for non-medical (e.g., recreational) purposes
Dosage	
DDD	"The assumed average maintenance dose per day for a drug used for its main indication in adults," as defined by the WHO
OME	The dose of an opioid expressed as the equianalgesic dose of oral morphine
Use patterns	
Chronic high-dose use	Continuous opioid use for more than 3 months with a dose greater than 90 OME
Misuse	"Opioid use contrary to the directed or prescribed pattern of use, regardless of the presence or absence of harm or adverse effects," defined by ACTTION
Abuse	"Intentional use of the opioid for a non-medical purpose, such as euphoria or altering one's state of consciousness," defined by ACTTION
Addiction	"Pattern of continued use with experience of, or demonstrated potential for, harm," defined by ACTTION. This definition captured a broader group than DSM-5 opioid use disorder and ICD-11 dependence

WHO, World Health Organization.

tween them, or define the source. Changes in mortality rates based purely on toxicological data can thus be difficult to interpret. This in turn has consequences for the interpretation of epidemiological data and for (data driven) policy responses.

Quantification of Opioid Consumption and Dosages

Opioid doses can be quantified in several different ways, most commonly in Defined Daily Doses (DDDs) or oral morphine equivalents (OME) [15–17]. Most national prescription databases report opioid consumption in DDDs, a unit recommended by the World Health Organization for drug consumption studies. DDD is defined as "*the assumed average maintenance dose per day for a drug used for its main indication in adults*" [16]. DDDs are, however, of limited value in quantifying and comparing different opioid doses because they do not fully reflect the relative potency of each individual opioid [15]. This limits the comparison of opioid use between countries where different types of opioids are used.

A more useful unit for comparing opioid doses is OME, which is calculated by converting the opioid dose to an equianalgesic dose of oral morphine. This makes a more clinically relevant comparison of doses for different opioids possible. The choice between DDD and OME can significantly impact study results. For example, in a study by Svendsen et al. [15], opioid use was either higher in Sweden or in Denmark, depending on the use of either DDD or OME as the unit of analysis. A limitation of OME is, however, that the conversion ratios for different opioids are not universally agreed upon and not all are supported by high-quality evidence. In addition, conversion ratios for individual patients can vary depending on, e.g., genetics and tolerance. Fortunately, Nielsen et al. [18] developed a comprehensive list that gives a single OME conversion ratio for the different pharmaceutical formulations and routes of administration of most opioids. This list was based on different international resources and can be used to calculate OME doses in a consistent way.

Patterns of Opioid Use

A lack of clear definitions for the different patterns of (prescription) opioid use and the diagnosis and registration of opioid-related harm results in large variations in outcome estimates in different studies. Epidemiological variation due to different definitions for patterns of (prescription) opioid use and opioid-related harm hinders valid evaluations and adequate (data-based) policy responses. Below we discuss these different definitions for patterns in (prescription) opioid use and opioid-related harm and propose ways to move forward.

Firstly, quantitative trends in opioid use are often examined using healthcare registration data, based on predefined patterns of opioid use. Results from such studies

are often difficult to interpret and comparisons with other studies are problematic if the definitions used to classify patterns of opioid use are different. For example, a systematic review by Jivraj et al. [19] on persistent postoperative opioid use found 29 different definitions for persistent opioid use in 39 studies. When these different definitions were applied to a single set of healthcare registration data, estimates for persistent postoperative opioid use in opioid-naive patients undergoing surgery varied more than 100-fold from 0.01% to 14.0% [19]. A review by Karmali et al. [17] also found a high variation in estimates of chronic opioid use, ranging from 1.3% to 25%.

A consensus definition for chronic opioid use and a uniform way to identify patients with chronic opioid use in registration data does not yet exist. However, several recommendations can be made based on the reviews by Jivraj et al. [19] and Karmali et al. [17]. Most importantly, chronic opioid use should be defined as continuous opioid use over a specific period of time. To identify this in a data set, preferably both the date and duration of prescriptions should be used. Most studies use 3 months as a cut-off value for chronic use, which is in line with clinical guidelines.

In addition to duration, opioid dose and route of administration are important factors to consider. Patients receiving high dosages are at greater risk of opioid-related harms such as addiction, overdose, and motor vehicle injuries [20, 21]. Consensus on the definition of high-dose opioid use is currently lacking. However, the CDC Guideline for Prescribing Opioids for Chronic Pain recommends avoiding opioid dosages over 90 OME. Route of administration is also highly relevant because routes have a different onset of action. Opioids with a fast onset of action (e.g., injections or nasal sprays) have a higher addictive potential [22].

Secondly, studies focussing on problematic prescription opioid use should distinguish between misuse, abuse, and addiction. Definitions for these types of problematic use often differ per study and sometimes overlap [23]. In order to standardize these definitions, Smith et al. [23] formulated mutually exclusive definitions for prescription drug misuse, abuse and addiction based on a literature review and consensus amongst the multidisciplinary Analgesic Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) working group [23, 24]. They defined misuse as "Opioid use contrary to the directed or prescribed pattern of use, regardless of the presence or absence of harm or adverse effects." This means that misuse includes higher and/or more frequent doses than intended by the prescriber, use of an opioid for pain reduction that was prescribed to another person, or use for a different medical indication than intended by the prescriber (e.g., for insomnia instead of pain). Misuse explicitly excludes non-medical use, which is categorized as either abuse or addiction. Abuse is defined as "Intentional use of the opioid for a non-medical purpose, such as euphoria or altering one's state of consciousness." Thus, abuse includes recreational opioid use, as well as opioid use to alleviate negative affect, independent of harm or adverse effects and is therefore different from the DSM-5 or ICD-11 diagnosis of opioid use disorder or addiction. This category also includes opioid abuse by proxies, which has been an important driver of opioid use in the US [25]. Finally, addiction is defined as a "Pattern of continued use with experience of, or demonstrated potential for, harm" (e.g., "impaired control over drug use, compulsive use, continued use despite harm, and craving"). Campbell et al. [26] empirically compared the ACTTION addiction definition with both ICD-11 dependence and DSM-5 substance use disorder definitions in patients using opioids for chronic non-cancer pain (CNCP). They found that the addiction definition captured a larger group of patients, showing fewer problem behaviours than the ICD-11 and DSM-5 criteria. Patients who only met the addiction criteria (and not ICD-11 or DSM-5 substance use disorder criteria) also had lower rates of psychological distress and substance use histories. Although a broad definition might be useful for epidemiological research and monitoring, it is less suitable for clinical practice since it could label people without problematic opioid use as addicted [26].

In addition to definitions for problematic opioid use, differences in measurement tools and the selection of populations deserve careful consideration. A review from Vowles et al. [24] found a broad range in opioid misuse in chronic pain patients (0.08%–81%), which was largely attributed to differences in study population selection and the measures of misuse that were used. The study with the highest rate was conducted in the USA in a population of chronic pain patients who presented to an emergency department seeking prescription opioid refills. Misuse was identified using a self-report questionnaire [27]. In contrast, the lowest rate was found in a Norwegian study which identified misuse in a nationwide prescription database using a definition based on opioid dose, duration, number of prescribers, and concurrent benzodiazepine use [28].

Thirdly, when investigating prescription opioid use, the medical indication should always be taken into con-

sideration because the often-reported increase in the number of opioid prescriptions is not necessarily problematic. For example, an increase in short-term opioid use could result from improved post-operative pain management since opioids are effective in reducing short-term pain after surgery [29]. Similarly, whilst opioid use for chronic cancer pain or palliative care is effective [30], for CNCP other types of therapies are preferred [21]. Consequently, an increase in prescription opioid use could indicate inadequate non-evidence-based pain management when opioids are used for CNCP, or in contrast improved pain management and care for patients with acute pain or during palliation in terminal care. Hence, the contextual information and strict clinical indications are important to correctly interpret the specific use of an opioid in medical practice. Improvements in pain care can otherwise be falsely interpreted as unwarranted over-prescribing.

Opioid Mortality

Between and within country differences in procedures used to establish cause-of-death statistics can significantly influence the number of registered overdose deaths, making opioid-related mortality rates within and between countries difficult to compare [31]. For example, in England, all unexpected deaths are investigated by a coroner, whilst in many other countries, this is less common. Since most drug-related deaths are classified based on toxicological screening, differences in post-mortem toxicological screening methods and policy can also influence the reported number of drug-related and opioid-related deaths [32]. For instance, in Sweden, the number of fentanyl-related overdose deaths doubled after the introduction of routine toxicological fentanyl screenings [33]. Similarly, a reanalysis of post-mortem blood samples in Germany focussing on prescription opioids, found a 3.4-fold increase in the number of fentanyl-related overdose deaths compared to standard screening procedures [34]. These examples indicate that death rates for rare or difficult to detect compounds are highly dependent on regional procedures and available technology and funding. Consequently, comparing national opioid-related death rates, and interpreting trends over time is only possible when detailed information on country-specific procedures and possible changes in these procedures over time are considered. Although the EMCDDA regularly reports opioid related mortality for the entire EU, the data are still based on the cause-of-death statistics from individual countries.

Drivers

Drivers of Prescription Opioid Use

Increasing trends in prescription opioid use have been described for several European countries, including Germany [35], France [36], the United Kingdom [37], Spain [38], Poland [39], and the Netherlands [40]. Different drivers may have contributed to this increase.

Firstly, an important factor that could contribute to an increase in opioid use is an ageing population with more chronic pain problems and palliative care. Between 2004 and 2016, the proportion of people in the EU older than 80 increased from 3.9% to 5.4% [41] and is likely to increase even further. In addition, physicians might be reluctant to prescribe NSAID painkillers to the elderly due to the fear for severe gastrointestinal, cardiovascular, and renal side effects [42].

Secondly, some prescription opioids, such as oxycodone and fentanyl, are not associated with the same stigma as for instance morphine [43]. Patients often associate morphine with addiction, terminal illness, and imminent death [44]. Patients may not recognize oxycodone and fentanyl as being in the same category as morphine, thus potentially contributing to their acceptance and increasing use. Moreover, many of these newer opioids were introduced as patches, nasal sprays, and lollipops, which might – mistakenly – be perceived as safer than tablets or injections by both patients and prescribing physicians.

Thirdly, marketing of oxycodone is often cited as an important reason for increased oxycodone prescribing, especially in the USA. However, in contrast to the USA, marketing of drugs directly to patients is prohibited in Europe. Still, oxycodone consumption also increased in Europe with 47% between 2004 and 2016 [10]. It is unclear whether and to what extent other types of pharmaceutical marketing, like pharmaceutical support in medical curriculum development, doctor visits by pharma representatives, and congress presentations have been driving this increase in Europe.

Fourthly, increased opioid prescribing may also have been fuelled by increased attention for pain management (pain as fifth vital sign) [45, 46], decreased acceptance of pain by patients, a lack of physician training in and access of non-pharmacological pain management (e.g., physical therapy or psychological support), and shorter or no in-hospital stay after certain surgical procedures. Whilst all these factors appear to be plausible drivers for the increased prescription opioid use in Europe, little research has been done to investigate their relative contributions.

Drivers of Illicit Opioid Use

Although heroin is still the most frequently abused opioid in Europe, there are a growing number of reports on the abuse of other – mainly synthetic – opioids. A notable example is Estonia, where IMF addiction has overtaken heroin addiction [46]. In 2012, 87% of patients entering treatment for drug addiction in Estonia listed fentanyl as their primary drug of abuse [47]. Another example is Southern Bavaria where diversion of fentanyl patches from legal sources caused a temporary increase in fentanyl overdoses between 2005 and 2014.

In the EU, methadone, buprenorphine, fentanyl, codeine, morphine, tramadol, and oxycodone abuse and dependence now account for 22% of all treatment-seeking primary opioid use disorder patients [48]. This suggests that opioid abuse and dependence in some European countries are shifting from heroin towards prescription opioids and illegally produced synthetic opioids. Interestingly, the sources of the fentanyl and the drivers for its illicit use can differ between countries. In Estonia, a decrease in heroin availability was the main driver for increased use of IMF and opioid-related overdose deaths [49]. Compared to heroin, IMF is easier to smuggle, has a lower cost per dose, and has a more reliable supply than heroin [50]. In contrast, in Southern Bavaria, the fentanyl involved in the increased opioid overdose rate was sourced from diverted fentanyl patches [51] and an increase in its prescription use was the main driver for its illicit use.

Diversion and doctor shopping, both considered illegal, may also play an important role as drivers of illicit opioid use. For example, a US study found evidence of drug diversion in more than half of all unintentional prescription drug overdose deaths. Receiving prescriptions from multiple prescribers (doctor shopping) was present in about a fifth of all opioid-related deaths [25]. Obtaining opioid prescriptions from multiple doctors is possible in the USA due to the decentralized healthcare system. The centralized and single-payer system in most EU countries make doctor-shopping more difficult and could limit the emergence of iatrogenic opioid disorders, opioid diversion, and opioid overdose deaths from prescription opioids.

Recommendations and Conclusions

Quantitative trends in prescription opioid use and misuse of illicit opioids in Europe are rather well described and serious concerns have been raised about the possible negative consequences of the increase in opioid prescribing in Europe. However, comparative research into the underlying drivers of opioid use and the related harm in Europe appears to be lacking. Further research is needed for the development of adequate monitoring and adequate policy responses.

Firstly, policy makers aiming to reduce availability of illicit opioids should distinguish between illicitly manufactured opioids and diverted prescription opioids. Both are manufactured by different means and reach the illegal marketplace via different routes. Research into the source of illicit opioids is thus needed for an adequate policy response. Examples of policy responses to prevent prescription opioid diversion are prescription monitoring programs to detect fraud, legislation to regulate prescribers [52], and the introduction of abuse-deterrent formulations such as combinations with naloxone or formulations that are difficult to crush and resist chemical extraction [53]. Actions aiming to reduce the availability of illegally manufactured opioids (e.g., heroine and IMF) are more in the realm of traditional law enforcement. Research on prescription opioid diversion is currently lacking, precluding any policy response.

Secondly, although heroin is still the most used illicit opioid, serious concerns have been raised about potential harms from prescribed opioid use in Europe. In some parts of Europe, the prevalence of heroin addiction is decreasing and addiction to other types of (prescription) opioids is increasing. Policymakers aiming to reduce harm from prescription opioid use could include risk-mitigation strategies for patients who have an increased risk for opioid-related harm, switching chronic opioid users to safer opioids such as (long-acting) buprenorphine (with or without naloxone), development of opioid-tapering guidelines and expanding treatment for iatrogenic opioid use disorders. In addition, adequate availability and accessibility of treatment for people with opioid use disorder should be provided, with special consideration given to patients with an iatrogenic opioid use disorder. Regions with high illicit opioid use should also implement adequate harm reduction strategies targeting this population (e.g., take-home naloxone kits or supervised self-injection rooms) [11, 12].

Thirdly, comparing data on opioid use and related harms within and across countries requires shared and meaningful definitions, distinguishing between non-problematic prescription opioid use and problematic opioid use. When examining problematic prescription opioid use, researchers should distinguish between misuse, abuse, and addiction/dependence. The latter can either be

defined broadly by using the ACTTION addiction definition or narrower and more clinically relevant by using ICD-11 dependence or DSM-5 (moderate/severe) opioid use disorder. When using healthcare registration data to investigate opioid use, careful consideration should be given to the definition of chronic opioid use. The definition should at least identify continuous use over a specific minimum period (e.g., >3 months) and include criteria for a minimum opioid dose (e.g., >90 OME). Opioid dose or consumption should preferably be expressed in OME, a clinically relevant unit that allows comparing doses of different opioids and different routes of administration.

Although we advocate the use of shared definitions, it must be acknowledged that researchers cannot always choose an ideal definition, especially when using data that were collected for a different purpose. For example, exact opioid doses and durations are often difficult to extract from healthcare registration data, which complicate the identification of chronic high-dose opioid use. In such instances, a distinction between the (shared) ideal definition for an outcome, and a practical definition for identifying this outcome should be made and reported explicitly. This optimises comparability of research on different types of data. In addition, limitations of the practical definition should always be discussed, including the direction of potential biases.

Fourthly, the specific procedures for establishing a national death statistic can greatly influence the number of opioid-related deaths that are found. Consequently, researchers interpreting and comparing opioid mortality should consider the methods used to establish the death statistic and discuss the direction of potential consequences.

Fifthly, studies on the drivers of increased opioid prescribing are needed because little is known about this topic, hindering policy responses aimed at reducing unwarranted prescribing of opioid painkillers. Examples of possible policy responses are (1) improving physician knowledge on pain treatment, (2) development of evidence-based prescribing guidelines, and (3) expanding the access to non-pharmacological pain treatments. Finally, sudden discontinuation of opioid treatment should be avoided since withdrawal symptoms may lead patients to seek out illicit opioids to ameliorate these symptoms [54]. Without better knowledge of the specific drivers of prescription opioid use, a targeted policy response is impossible.

Sixthly, comparable to the CDC in the USA, the EMCDDA should expand its monitoring and reporting of opioid-related harm in Europe, and specifically make a distinction between illicit and prescription opioids. Monitoring of prescription opioid-related harm should include rates of misuse/abuse, diversion of legal prescription opioids into the illegal marketplace, treatment demand for iatrogenic opioid addiction, and mortality from prescription opioids.

Finally, we must recognize that there are many indications for which opioids provide unparalleled pain relief. Policy aimed at reducing unwarranted opioid prescribing or related harm should not, as a side effect, get in the way of opioid prescribing for patients with severe cancer pain or acute post-operative pain.

In summary, shared and meaningful definitions for prescription opioid use and related harms are needed to understand the opioid situation in Europe. Knowledge of the country-specific drivers for the increased opioid use and related harms is needed for an adequate policy response. Continuous close monitoring is warranted to guarantee early warnings and take timely actions. Finally, physicians should take a balanced approach to prescribing opioid pain killers, not avoiding them when there is a proper indication, without prescribing them too easily without full awareness of their potential risks.

Conflict of Interest Statement

W.v.d.B. reports personal fees from Angelini, non-financial support from Camurus, personal fees from Takeda, personal fees from Opiant, personal fees from Indivior, non-financial support from D&A Pharmaceuticals, outside the submitted work. A.S. is an Editorial Board Member of European Addiction Research. All other authors have nothing to disclose.

Funding Sources

This research was supported by a Junior Researcher Grant 2018 of the Radboud University Nijmegen Medical Centre. The study sponsor had no role writing or the decision to submit the paper.

Author Contributions

G.K., A.S., and W.v.d.B. conceptualized the paper, and drafted and revised the manuscript. M.P., F.A., K.V., H.S., R.v.D., and C.K. provided critical input and discussion for the manuscript.

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