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COMMENTARY

A Framework for a New Paradigm of Opioid Drug Tapering Using Adjunct Drugs

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Abstract: The misuse of and dependency on prescription opioids represents a significant crisis at the national level, impacting not only the health of the public but also the societal and economic well-being. There is a critical need for strategies to reduce the dosage of prescribed opioids to limit opioid-associated adverse effects and lower the risk of addiction development in patients experiencing chronic pain. Opioid-sparing medications, when co-administered with opioids, enable a reduced opioid dose without loss of efficacy. This suggests the potential for using opioid adjunct drugs in opioid tapering, whereby opioid doses are lowered incrementally in a systematic manner to improve a patient's safety profile or quality of life. The objective of this report is two-fold: 1) to illustrate the potential for adjunct drugs in opioid tapering, and 2) to describe the steps needed to be taken to develop a framework for the use of adjunct drugs in opioid tapering. This can provide the impetus for further investigation into opioid tapering and the development of improved clinical care. The proposed project implements knowledge synthesis methods to develop the framework for a new paradigm of opioid drug tapering that incorporates opioid dosage reductions with adjunct drugs. Framework development is organized into three major phases: 1) Adjunct drug characterization, 2) Assessment of the opioid-sparing effect, and 3) Usability of data for clinicians. The knowledge gained from this project can provide a foundation for improved analgesia protocols for opioids and adjunctive drug therapy.

Keywords: opioid adjunct, opioid-sparing, opioid tapering, addiction risk, knowledge synthesis

Introduction

The Centers for Disease Control and Prevention (CDC) cites various approaches to mitigate the widespread opioid crisis and avert opioid use disorder (OUD).[1] Opioids, commonly prescribed for managing moderate to intense pain, carry a risk of adverse effects, which may include sleep disturbances, depressive symptoms, constipation, cognitive impairment, drug dependency, and premature mortality.[2] To prevent these issues, strategies typically focus on educational initiatives promoting judicious use of opioids, discouraging misuse, and systematic surveillance of opioid prescriptions through drug monitoring programs. The effectiveness of these and other preventative measures has yet to be fully determined.[3]

Many patients, especially those with long-term pain conditions, are often given prescriptions for opioid medications. These individuals typically need to take these potent analgesics in high doses over extended periods to manage their pain effectively. In 2020, the overall opioid dispensing rate was 43.3 prescriptions per 100 people, a total of more than 142 million opioid prescriptions.[4]

The misuse and dependence on prescription opioids present a significant challenge that impacts the nation's health, societal, and economic stability. The CDC estimates that the annual economic impact of this issue in the US is around $78.5 billion. This figure encompasses healthcare expenses, reduced workforce efficiency, expenditures for addiction rehabilitation, and the costs associated with law enforcement and legal proceedings.[5] Accordingly, there is a critical need for strategies to reduce the dosage of prescribed opioids to limit opioid-associated adverse effects and lower the risk of addiction development in patients experiencing chronic pain.[6]

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Utilizing adjunctive pharmacotherapy alongside opioids presents a viable strategy for mitigating the detrimental impacts of opioids. As stated by Khan et al, this involves the use of a drug "that has been found in clinical practice to have either an independent analgesic effect or additive analgesic properties when used with opioids".[7] Medications that spare the use of opioids, when used alongside opioids, permit the lowering of opioid dosage without diminishing their effectiveness.[8] Essentially, these adjunct drugs facilitate comparable pain alleviation for the patient while minimizing the quantity of opioids required.[9]

To illustrate, in a prospective, randomized, double-blind, controlled trial on the treatment of background pain in burns, the opioid-sparing effect of lidocaine was assessed and found to be significant. Results indicate that during the study's duration, there was an approximate 25% reduction in the measured value of opioid consumption.[10]

This suggests the potential for using opioid adjunct drugs in opioid tapering, whereby opioid doses are lowered incrementally in a systematic manner to improve a patient's safety profile or quality of life. Essentially, a well-executed tapering plan is a collaborative effort that may lead to a reduction in the daily dosage or complete cessation of opioid treatment, based on the individual objectives and risk assessment of the patient.[11]

According to the CDC,

> opioid tapering should be individualized and should minimize symptoms of opioid withdrawal while maximizing pain treatment with nonpharmacologic therapies and nonopioid medications.[12]

In general, the CDC advises that for individuals who have been on opioid therapy for over a year, a gradual reduction of the dosage by 10% each month is a viable starting point. For those whose opioid use spans a shorter duration, ranging from several weeks to months, it may be appropriate to consider a 10% reduction weekly. Other healthcare organizations have suggested incremental dosing reductions for opioid tapering in a similar manner.[12–14]

Clinicians may have difficulty developing a tapering strategy with patients due to insufficient knowledge of which nonopioid medications have been shown to be most effective at supporting a successful opioid taper.

The objective of this report is two-fold: 1) to illustrate the potential for adjunct drugs in opioid tapering, and 2) to describe the steps needed to develop a framework for incorporating adjunct drugs into the process of gradually reducing opioid dosage through tapering. This, in turn, can provide the impetus for further investigation into opioid tapering with adjunct drugs and the development of improved clinical care.

Questions about the appropriate use of adjunct drugs in opioid tapering have not been sufficiently answered by existing studies or research within the field of pain management. The "research gap" needs to be addressed through empirical studies; the proposed framework seeks to provide the backdrop for this.

In this report, a project is described—essentially a call for action—whereby the potential of adjunct drugs for opioid tapering is highlighted. If proven successful, this can lead to a new clinical treatment paradigm for opioid drug tapering that incorporates opioid dosage reductions using adjunct drugs.

To our knowledge, the use of adjunct drugs in opioid tapering is not a formally accepted practice among clinicians and potentially can offer advantages for opioid tapering compared to reductions in opioid dosing alone. As is the case with many interventions designed to improve medical care, the project described in this report can lay the groundwork for developing a prescribing guidance document[15] for safe and effective opioid tapering with adjunct drugs based on the best available evidence. With reference to the two-fold objective of this report, implementing the project requires the completion of specific tasks, and one rendition of how this may take place is described in the subsequent sections.

The Potential for Adjunct Drugs in Opioid Tapering: Scope of the Relevant Literature

A search of the medical database PubMed revealed the number of research reports that have been published on opioids and adjunct drugs (Figure 1). The points on the graph represent individual research on the efficacy of opioid adjunctive drug therapy. A closer analysis of results from completed research studies can inform patients and caregivers about treatment options. This concept is captured by the research method of identifying, selecting, and analyzing results from multiple studies. Literature searches by the authors have revealed over 118 reports on opioid adjunct drug therapy, studies, which were conducted in a multitude of formats.[16] Types of studies with frequency of occurrence include: Randomized Control Trial (76),

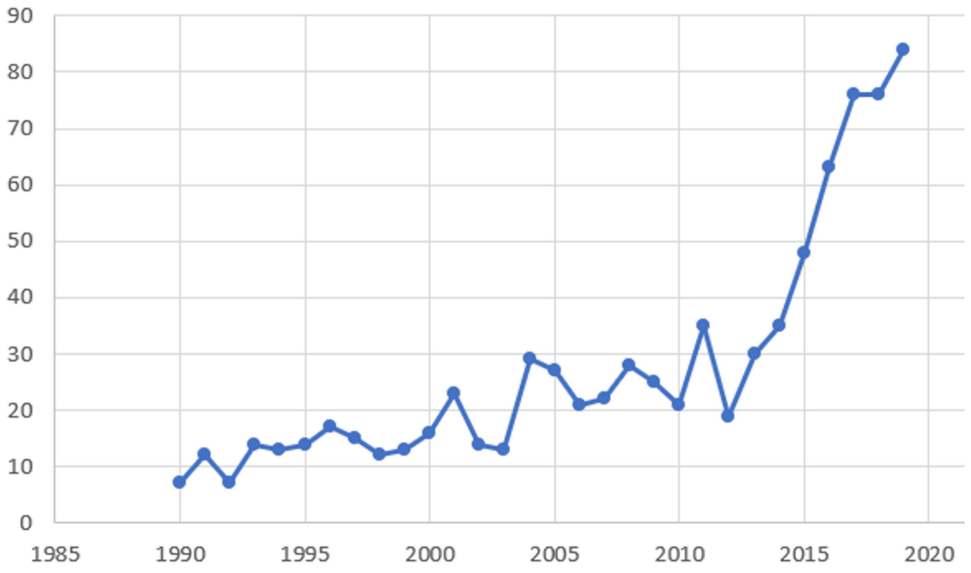

Figure 1 PubMed articles published on Opioids and Adjunct Drugs by Year [16].

Systematic Review (10), Retrospective Cohort (9), Narrative Review (7), Meta-Analysis (5), Prospective Cohort (3), Cross-sectional (2), Case Report (2), Case Series (2), Journal Conference Abstract (2), Prospective and Retrospective Cohort (1).

Examination of the individual studies has identified specific opioid drugs used in adjunctive therapy with magnitude of occurrence (Figure 2) and specific adjunct drugs used in opioid adjunctive therapy with magnitude of occurrence (Figure 3).[16]

Research on opioid adjunctive drug therapy is extensive and ongoing. Compiling and analyzing this information, ie, "synthesis", to identify and summarize evidence, will enhance the generalizability and applicability of research findings. An essential element of the project will consist of the exploration of the direction of the associations between opioid adjunct therapy and health outcomes, particularly with multiple drugs, using empirical evidence drawn from research reports and other sources of valid information.

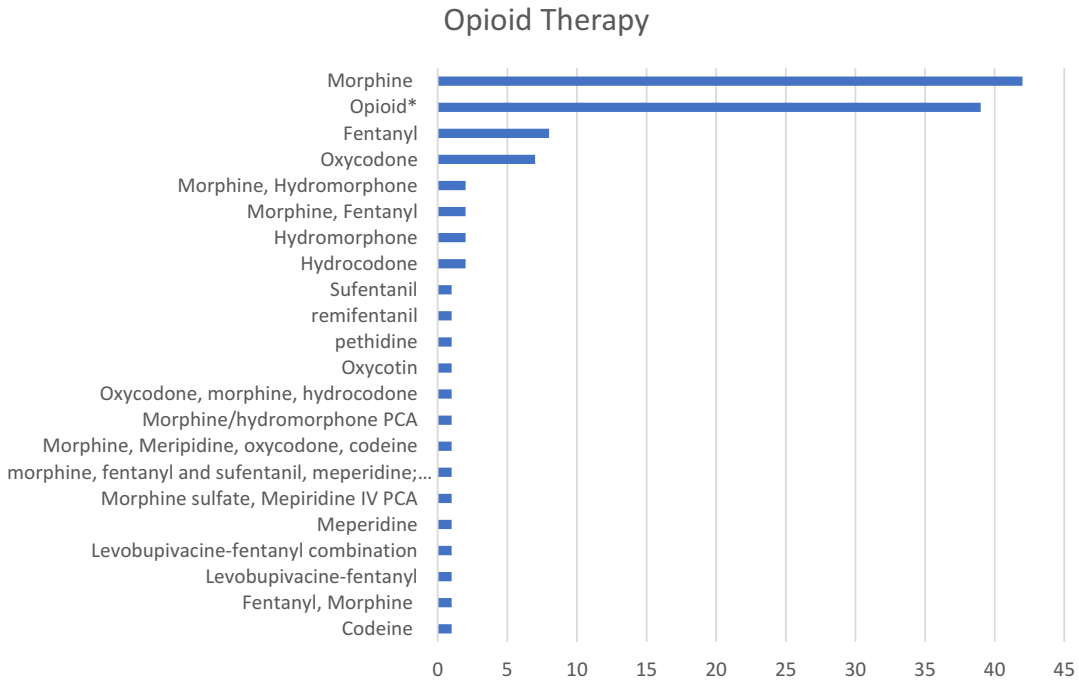

Figure 2 Opioids used in adjunctive therapy.

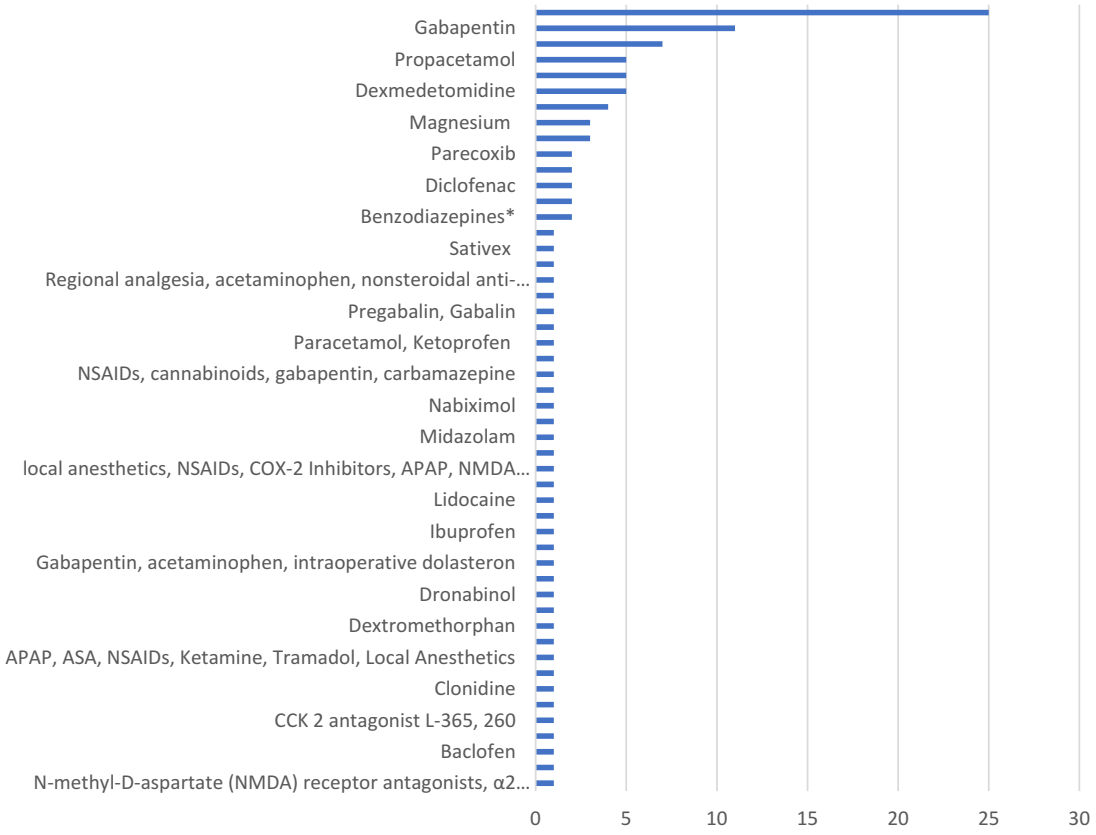

Figure 3 Adjunct drugs used in opioid adjunct therapy.

Developing a Framework for the Use of Adjunct Drugs in Opioid Tapering

Framework development may be organized into three major phases, which also may serve as information goals for the successful completion of the project. The phases include: 1) Adjunct drug characterization, 2) Assessment of the opioid-sparing effect, and 3) Usability of data for clinicians. In the following section, each phase is described in greater detail.

Adjunct Drug Characterization

Whereas a scope of the relevant literature revealed a significant number of research reports on opioids and adjunct drugs, to determine the potential in opioid tapering, further characterization of the drugs is needed. Medication characterization involves the following:

- Comprehensive precise identification of the drugs, doses, and administration schedules of adjunct drugs used in combination with opioids for treatment of major types of non-cancer pain to include potential agents for opioid tapering.

Assessment of the Opioid-Sparing Effect

- For application to opioid tapering, accurate determination of the opioid-sparing effect is needed for the identified adjunct drugs used in combination with opioids.

The therapeutic role of adjunct drugs as co-analgesics is

to increase the therapeutic index of opioids by a dose-sparing or opioid-sparing effect, add a unique analgesic action in opioid-resistant pain, or reduce opioid side effects.[17]

Evidence indicates that using opioid-sparing analgesic protocols post-operatively is a viable alternative to conventional opioid-based pain management.[18,19]

Abdelrahman et al offer a method to define opioid sparing which serves to illustrate how this effect can be quantified.[10] Here, opioid-sparing is defined as a decrease in opioid consumption with adjunct drug therapy compared to opioid dosing alone during a specified time period. The opioid dosing may be based on either standard recommended dosing guidelines for opioids or baseline dosing of an opioid specified in a particular study, where the baseline dosing is based on the clinical judgment of the clinician. The opioid-sparing is expressed as a percentage change in milligram amounts of opioid dose.[10]

For uniformity in reporting, it is necessary to convert the opioids identified in the project to Morphine Milligram Equivalents (MMEs). An MME is defined as

> the equivalent number of milligrams of morphine that an opioid dose is equal to when prescribed. Calculating MME accounts for differences in opioid drug type and strength.[20]

The computation of MMEs will be based on the established medical guidelines provided by MDCalc.[21]

Usability of Data for Clinicians

- For clinicians, data must be organized and presented in a format that is accessible, usable, and applicable to help address patient needs. This may take the form of a prescribing guidance document[15] for safe and effective opioid tapering with adjunct drugs.

As opioid tapering, in general, involves a systematic process of reducing opioid doses, this proposed guidance document involves the incorporation of adjunct drugs in the process.

The suggested design of the document would emulate the format and level of detail specified by the current CDC Guideline for Prescribing Opioids for Chronic Pain, which also serves as a reference standard for the project.[22] In the section "Clinical Practice Guideline Development Methods, Systematic Reviews and Evidence Sources" the types of analyses that center around the conduct of systematic reviews are described. The project incorporates these research methods and expands the CDC methods to include Case Reports and other forms of evidence in addition to Randomized Controlled Trials (RCTs).

In addition, the content of the guidance document will emulate the American Society of Health-System Pharmacy criteria for drug therapy guidelines, which include

> indications, dosage regimens, duration of therapy, mode(s) of administration, monitoring parameters, and special considerations for the use of a specific medication or medication class.[23]

To enhance user experience, the document could be formatted as an interactive dashboard. This format would enable the delivery of up-to-date information, aiding in decision-making processes during patient care and potentially leading to better health outcomes.[24]

Methods

This project is about the discovery, development, communication, and application of knowledge in the specific aspect of treatment for opioid misuse and drug tapering. To achieve the project goals, which include identifying adjunct drugs for opioid tapering and framework development, a comprehensive synthesis of knowledge and evidence is needed.

Knowledge synthesis is "a research methodology within health care delivery science and a critical initial step in knowledge translation".[25] The significance of knowledge syntheses in the scientific community is becoming more evident, as they are now seen as substantial scholarly works. Notably, these syntheses tend to receive more citations compared to different types of research designs.[26] Additionally, they serve as a foundational element for various evidence-based tools. Most organizations that develop guidelines advocate for the inclusion of knowledge syntheses as a fundamental component of the process.[27]

Through the application of clear and structured techniques, retrospective analyses can pinpoint, choose, and rigorously assess pertinent studies. Additionally, these methods facilitate the gathering and examination of data derived from reports grounded in evidence. When suitable, statistical tools can be employed to evaluate and encapsulate the findings from the collected reports.

Target Searches

The opioids targeted for initial analyses have the highest risk for misuse: hydrocodone, oxycodone, tramadol, codeine, and morphine. In 2017, it was reported that approximately 110.4 million prescriptions for opioids were dispensed to outpatients, accounting for 3.8% of the total 2.9 billion prescriptions filled for adult patients across the United States. The most frequently prescribed opioids, in order of the number of prescriptions filled, included hydrocodone with 45.9 million, oxycodone with 26.8 million, tramadol with 21.6 million, codeine with 6.1 million, and morphine with 4.5 million.[28]

Protocol

A protocol has been developed based on recommendations from the leading organizations in knowledge synthesis: The Mayo Clinic,[25] The Canadian Institutes of Health Research,[29] and The Cochrane Organization.[30] A Cochrane Review is "a systematic, up-to-date summary of reliable evidence of the benefits and risks of health care. intended to help people make practical decisions". Evidence suggests that the methodologies employed by Cochrane are highly effective in producing dependable and current insights into effective healthcare practices.[31] Searches for reports will include published research, abstracts, and "gray" literature.

As described by Chalmers[32] and Pope, Mays and Popay,[33] the synthesis process encompasses these subsequent stages: "1) Stating the objectives of the research; 2) Defining eligibility criteria for studies to be included; 3) Identifying (all) potentially eligible studies; 4) Applying eligibility criteria; 5) Assembling the most complete data set feasible, including, data extraction; 6) Quality appraisal of included studies; 7) Analyzing this data set, using statistical synthesis and sensitivity analyses, if appropriate and possible; and 8) Preparing a structured report of the research." In the context of the proposed project, each step is described in Appendix A.

The proposed project focuses on creating a new body of knowledge by drawing on search methods and technologies at the forefront of knowledge synthesis. The intent is to conduct a comprehensive review and integration of all research findings regarding the efficacy of adjunctive opioid medication treatments. This endeavor aims to ensure the evidence is applied responsibly and effectively in strategies for reducing opioid use.

The impetus for engaging in research that synthesizes knowledge stems from the understanding that scientific progress is built incrementally, with each study contributing to a larger body of work. Rarely does a single study influence changes in procedures or guidelines.[34] Individual studies can sometimes present biased results due to random variation or systematic errors.[35] In contrast, the process of synthesizing knowledge is a robust scientific technique that compiles and evaluates evidence, enabling the evaluation of the applicability and uniformity of research outcomes, as well as the investigation of any discrepancies in the data.[36] Moreover, the systematic methodologies employed in these syntheses serve to curtail bias, thereby enhancing the reliability and accuracy of the findings.[35]

Results and Expected Outcomes

It is anticipated that the project will result in drug therapy guidance recommendations to aid transparent decision-making for opioid tapering with opioid and adjunctive drug therapy.

A thorough examination of the evidence - The systematic and comprehensive content analysis of reports in aggregate with established scientific techniques - will reveal optimal drug combinations and dosing and administration schedules of opioids and adjunct drugs for opioid tapering. This, in turn, provides "actionable insights" for the use of these agents as a means for opioid tapering and prevention for Opioid Use Disorder (OUD).

The proposed research provides a "dynamic" systematic review - an ongoing review process that systematically integrates new and pertinent findings as they emerge. This knowledge, in the form of a guidance document, will be

embodied in a decision-making tool for access by clinicians and researchers in pain management. Presently, such a guidance document does not exist in our healthcare system.

Information Accessibility

As described previously in the section on the three major phases of framework development, an integral part of the framework includes usability and accessibility of information, whereby clinicians will have the ability to access opioid adjunct drug tapering information via a dashboard.[24] The dashboard consists of an interface with menu choices for the user to enter clinical criteria (patient demographic information, type of pain, etc). The user may query the system via an interface engine, and based on the criteria entered, drug therapeutic recommendations on opioid adjunctive drug therapy relevant to opioid tapering are returned. With the many data sources available, the dashboard will function as a data repository and information resource, a place where data is consolidated from various clinical sources, centralized in one system, available to use, and organized in a logical manner. The recording of practitioner transactions on drug regimens can provide insights into best practices for clinicians.

The dashboard will feature a variety of content such as written information, tabular data, and visual representations like charts and graphs, all sourced from universally recognized data formats and protocols. This is part of a comprehensive, evolving system for reviewing data that encompasses regular monthly searches of relevant literature, ongoing meta-analytical processes, and a web-based interface for reporting findings through the dashboard.

It is anticipated that the outcomes of this project will inform current and future clinical practice decisions and behaviors, which will encourage healthcare providers and their patients to prioritize treatments that are both safer and more efficacious. The goal is to enhance patient health indicators such as reduced pain and improved function, while concurrently curtailing the incidence of opioid use disorder (OUD), overdoses, or other detrimental consequences associated with these medications.

Results of the proposed project have the potential to create a new paradigm of medication prescribing with opioids and adjunctive drugs for opioid tapering. Clinicians will be able to access opioid adjunctive drug therapy guidance supported with evidence of effectiveness to safely improve analgesia in patients with chronic non-cancer pain. In addition, changes in prescribing patterns involving the optimal combination, dose, schedule, and administration of adjunct drugs with opioids will provide new insights into the use of opioid adjunct drug therapy for opioid tapering and as an effective preventative strategy for further development of OUD.

The project can provide the types and sources of evidence on opioid adjunctive drug therapy to inform practice, policymaking, and related research. The gathering and integrating of research will inform explanatory models to help make sense of related studies, as the cumulative results of studies are much more complex than the results of any single study. The schemes will be novel, having never appeared in previous theorizing or research. Findings will be presented in innovative fashion, culminating with development of an interactive dashboard tool with keyword search capabilities that enables user inputs and displays the associated output in a usable format for clinicians. A major benefit will be to inform clinical decisions and provide timely information at the point of care, which can effectively improve patient outcomes.

Discussion

At present, opioid-sparing with adjunct drugs is not widely used, although once it is embraced more fully by the medical community, it has the potential to be highly beneficial. In many cases, opioid-sparing with adjunct drugs may be a better pain management approach because it considers several different pathways for pain relief, and that could result in a more comprehensive solution for patients.[17,37]

Opioid-sparing effects with adjunct drugs for opioid tapering has been proposed,[38] however, the specific manner by which this should take place has not been made clear and warrants further investigation.

Reasons to Consider Tapering of Opioids

The expectation of pain relief treatment is to enhance not just the patient's ability to function, but also their overall well-being. The challenges associated with administering opioids are recognized in various medical environments. From the perspective of the healthcare provider and the patient, several reasons exist to consider an opioid taper.

Opioids are frequently utilized as a prescription for pain management after surgical procedures, in the event of injuries, or for managing specific medical conditions. As an illustration, it is imperative for surgeons to strategize the gradual reduction of opioid usage following surgical procedures, coinciding with the alleviation of immediate post-surgical pain. Similarly, oncologists might consider it essential to commence and oversee the process of tapering off opioids for individuals whose cancer is in remission and who may not require or derive advantage from ongoing opioid therapy.[39] In cases where patients undergo consistent increments in their opioid dosage or a change in their opioid prescriptions without a corresponding enhancement in pain relief, it is recommended to gradually reduce the dosage.[40]

Safety, Hyperalgesia, Tolerance, Stigma, Screening

Another valid reason for clinicians to taper opioids is safety risk. The numerous opioid-related adverse effects may prompt patients and providers to reevaluate the risks versus benefits of opioid therapy. As described to previously, these effects may include, but are not limited to, "cognitive compromise or sedation, refractory constipation, concerns about respiratory depression, hypogonadism, and osteoporosis".[41] Additionally, a condition exists identified as "opioid-induced hyperalgesia", which suggests that prolonged use of opioids may lead to heightened sensitivity or pain perception in some individuals.[42–44]

Patients experiencing opioid tolerance, such as those who have been receiving a daily dosage of 60 mg or more of oral morphine equivalents for at least one week, post-surgery, are generally advised to gradually decrease their medication intake to prevent symptoms of opioid withdrawal.[22]

In addition to the potential health risks with opioids, the societal stigma surrounding the use of these drugs also presents a concern that could justify the gradual reduction of their use. In general, the societal stigma attached to drug addiction frequently leads to adverse negative perceptions and judgments that can be a barrier to treatment and hinder individuals from seeking necessary treatment.[45]

In the workplace, the use of opioid treatments might be restricted, and it is common practice for employers to conduct regular toxicological urine tests.[46] In these circumstances, opioid tapering may help alleviate these associated stressors for patients.

Approaches to Tapering of Opioids

Medical professionals, particularly those with specialized expertise, may employ distinct methods for the gradual reduction of opioid dosages. Each patient requires a tailored approach, as no universal strategy fits all cases.[47] Furthermore, evidence in the literature on the appropriate dosage and timing for tapering opioids is ambiguous, with a range of recommendations found in different clinical guidelines.[48–52]

Recommendations by which opioid doses should be decreased and the time intervals for these reductions can vary widely. The approach may differ based on the type of opioid and the initial dosing levels. A widely used pain management source recommends a gradual decrease of 10% to 20% per day in the opioid dosage, which is generally acceptable for the majority of patients. It is also noted that the risk of experiencing withdrawal symptoms can be minimized if the dosage is reduced by no more than 25% of the patient's regular daily intake.[53]

In general, opioid tapering should involve a gradual decrease in the daily number of opioids administered, adjusted at designated intervals, with consideration given to the type and dose of opioids the patient is taking as well as the duration of their opioid exposure. If a patient's pain intensifies or they exhibit symptoms of withdrawal, the plan for gradually reducing their medication can be adjusted, and the tapering schedule can be modified with appropriate adjunctive therapy.[41,47] In addition, often it is necessary to prepare patients, particularly especially if patients are psychologically dependent on opioids or have a comorbid psychiatric condition.[11] The goal is to ensure that patients successfully reduce or discontinue opioids in a manner that does not lead to other prolonged adverse conditions. This may be accomplished with appropriate adjunctive therapy.

Limitations and Barriers to Implementation

The development of an optimal tapering regimen using adjunct drugs is not without challenges. Common barriers to the implementation of interventions designed to improve medical care have been identified and are applicable to opioid

tapering with adjunct drugs. The challenges faced encompass the difficulty in altering the established model of practice, encountering opposition and critical feedback from colleagues, and a reluctance to rely on evidence or research findings. Additionally, obstacles deemed significant may stem from an absence of recent evidence, the unavailability of definitive answers to clinical questions, and contradictory or inconsistent information in the scientific literature.[54]

Conclusion

This report offers insight into treatment options for patients impaired from opioid use, specifically regarding opioid tapering with adjunct drugs. In practice, the benefits of the framework described in the report cannot be fully realized until borne out through a demonstration of effectiveness, such as through case studies or clinical trials.

It would be beneficial for clinicians to have access to all available options for opioid tapering. Experts attest that for any patient, extended use of opioid medications can result in the development of a dependency, potentially manifesting as quickly as within a week of regular administration. A suitable strategy for managing opioid pain relievers should encompass the cessation of these medications when deemed appropriate.[41] In the event that discontinuation of opioid analgesics becomes necessary, an approach that limits adverse experiences for patients is of paramount importance, and tapering with adjunct drugs may be appropriate.

The knowledge gained from this project can provide a foundation for improved analgesia protocols for opioids and adjunctive drug therapy. In addition and importantly, this project can inform safe and effective prescribing practices for opioids and adjunctive drug combinations for use in opioid tapering. This could have a profound impact on minimizing the detrimental effects of prescription opioids, not only in our healthcare system but in society at large.

Disclosure

The authors report no conflicts of interest in this work.

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