Co-occurring disorders and the need for a research network

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The treatment of patients with pain and co-occurring disorders presents a significant knowledge gap that necessitates a strong infrastructure for conducting representative clinical trials. Norm Buckley from the Michael G. DeGroote Institute for Pain Research & Care explains

Rational treatment of patients experiencing chronic pain along with co-occurring disorders represents a huge gap in our body of knowledge. The solution includes infrastructure to support clinical trials targeting a population representative of patients who experience chronic pain.

This is a call for the creation of a robust infrastructure for conducting clinical trials in which chronic pain care is provided to patients with complex clinical problems. This is essential if we are to effectively treat the actual patients that come to our clinics.

The complexity of pain

As clinicians, we strive to deliver treatments to our patients that are grounded in robust clinical evidence and have a predictable outcome. Armed with this information, we can properly inform our patients of the likely course of events and warn them of potential deviations from the normal course of recovery. However, the current state of chronic pain literature and associated areas does not permit this in several areas of treatment. Even more unfortunately, the contingencies that drive clinical trials mean that it is unlikely the most useful trials addressing complex patient problems will be conducted in the absence of funding and infrastructure supported by health agencies rather than for-profit entities.

We begin with the understanding that pain is a complex phenomenon, and chronic pain is an interaction among biological processes, psychological processes, personal experiences, and the social milieu in which the patient exists. Optimal treatment of chronic pain will address all of these areas in concert.

In the 1990s, Johns Hopkins Medicine Division of Internal Medicine and the Journal of the American Medical Association [JAMA] published a series of articles outlining a step-by-step guide to critical appraisal of the scientific literature for clinicians. This was based on work initiated by Dr David Sacket and others at Canada's McMaster Medical School in their groundbreaking work on what came to be called 'Evidence based Medicine'. The group lists a series of questions to ask yourself before deciding if the information contained in a paper, guideline, or other publication is relevant to you. After examining the

rigor of the methodology to ensure that the trial was conducted and interpreted appropriately, a crucial question arises: ‘Does the trial population reflect my clinical practice?’

Discrepancies between real-world and clinical trial data

Sadly, in the overlapping worlds of chronic pain care, mental health, and addiction treatment, it is very unusual to find a trial population that resembles the patients we see day to day. Our patients often experience multiple issues, and frequently, the issues that most concern us in our care are also those most likely to disqualify a patient from participation in a new drug, device, or intervention trial. Drug trials often specifically exclude those patients who are experiencing illnesses other than the one being studied; patients with psychiatric disorders or addiction are excluded from almost all trials apart from those aimed at their condition. Even in psychiatric trials or addiction studies, a patient who also experiences another condition – for instance, a patient in a schizophrenia trial who is also living with depression – is likely to be excluded from participating. This exclusionary practice is also evident in behavioral intervention programs. For example, group-based anxiety treatment programs often exclude patients who suffer from chronic pain or depression, thereby limiting access to comprehensive care for those with complex clinical profiles.

Many of these decisions can be understood in the context of research, hypothesis testing, or the need for clarity about the effect of certain drugs or treatments. In a new drug trial, the group testing the drug wishes to avoid complications of any sort that may occur during treatment. So, all conditions except the one under study will be avoided in patients entering the trial. To clearly test a hypothesis, it is helpful to construct a trial design that allows the hypothesis to be tested in the most expeditious manner possible, examining the smallest number of patients that will still be sufficient to answer the question. This means that conditions that may unpredictably affect the patient’s health or may be associated with a worse outcome will be avoided. Including more clinical characteristics in a trial population may also necessitate a trial structure that stratifies subjects into multiple groups. This will increase the number of participants required and thus the cost of the trial. With a simpler trial design and a focused clinical population, the trial results can be interpreted clearly with respect to the specific question under consideration.

Unfortunately, most of our patients do not experience single disorders. It is common for a patient with chronic pain to also suffer from depression or anxiety. Approximately 10% of patients who are prescribed opioids for chronic pain will develop an opioid use disorder. And yet we know that treatment programs for opioid use disorder are much less effective for patients who also have chronic pain. Part of optimal treatment for chronic pain is physical activation and reversal of the social isolation that often accompanies chronic pain. However, the patient who also suffers from depression may have greater difficulty in participating in activation programs or social interactions because they have withdrawn from social contact due to their depression.

During the development of the 2017 and 2024 versions of the Canadian Opioid Guideline for use of opioids in the treatment of chronic pain, the advisory panels identified 24 questions that would be important to provide guidance for clinicians in using opioids to treat patients with chronic pain. Unfortunately, the research team was only able to find sufficient published clinical trials to address 11 of those questions. In those 11 questions, significant knowledge gaps remained, to the point that for five of the questions, the evidence supported at best a conditional recommendation. Conditional recommendations suggest that the evidence is not clearly in favour of or against an action, but rather that there are risks and benefits that must be considered in light of the patient's and their clinician's values and preferences. For the remaining 13 questions, there was simply insufficient published evidence to support any recommendation, and clinicians are left with the need to conduct empirical trials of care, attending to the individual response of the patient, but without any confidence in predicting the likely outcome.

A call for an independently-funded research network

Part of the argument for an independently funded research network and process is that a very large proportion of clinical trials are conducted at the direction of pharmaceutical companies, primarily for the development and approval of new drugs. Their focus is on identifying a product that has a specific indication and has a beneficial effect on that condition, with few, if any, adverse events associated with the drug. For reasons discussed above, this means that the drug's trial population will be restricted, and as unlikely as possible to experience adverse events, whether drug-related or not. It is helpful to avoid adverse events that are not drug-related but may complicate the interpretation of the study results or even become associated with the drug in a negative way. Trials addressing complex issues in complicated populations will need to be larger and will be harder to interpret because the subjects may be on other medications for their other conditions. These other medications may interact with the study drugs in unpredictable ways.

Research is undertaken to understand a health problem, to identify and test a new treatment, or to compare treatments. New drug research is driven by both the hope of improved treatment and the possibility that a new treatment can generate substantial revenue for the pharmaceutical researcher and manufacturer. Other research is undertaken by academics driven to understand a clinical problem and or to test new treatments. In the case of chronic pain, many treatments considered most effective do not generate significant revenue streams. Much clinical work by physiotherapists or psychologists, whose disciplines are responsible for providing much of the effective interdisciplinary care for patients with chronic pain, is delivered essentially as a 'trade' type profession, or artisanal service, one-on-one, or at most in small groups. The revenue streams generated in this manner do not lend themselves to supporting large research and discovery programs, unlike commercial firms that support R&D through the investment of portions of their revenue streams. In Canada, many services effective for managing chronic pain are not necessarily made available under the umbrella of the universal healthcare system. For example, psychological services and physical therapy

are often available through third-party insurance providers, and these services are dependent on employment status or the attainment of sufficient personal wealth. These services are viewed as costs rather than a potential source of wealth, and there is no well-organized driving force positioned to benefit from a better understanding of these interventions and the wider dissemination of the services themselves.

So, we would argue that the great need at present is to establish a national network of clinical trial sites where patients with complex conditions are being treated. We need to gather data systematically about their natural history and responses to existing treatments, and we must conduct trials, using established or novel methodologies, of new interventions, combinations of therapies, and new drugs or drug combinations. This is critical if we are to address the problem of chronic pain and other complex problems such as addiction and mental health issues.

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