Health Canada Santé Canada

Scientific Advisory Panel on Opioids (SAP-Opioids)

Record of Proceedings

November 15 & 16, 2016

Panel members: Jason Busse (Chair), Feng Chang, Lynn Cooper, Andrea Furlan, David Juurlink, Pamela Leece

Health Canada presenters: Léo Bouthillier, Patricia Carruthers-Czyzewski, Jiazhen Minnie Dai, Tanja Kalajdzic

Institute for Safe Medication Practices (ISMP) Canada presenter: Sylvia Hyland

Health Canada staff observers: Rita Beregszaszy, Marc Berthiaume, Léo Bouthillier, Louise Chrétien, Jiazhen Minnie Dai, Anne Decrouy, David Eng, Michael Haber, Nadia Giancaspro, Jacinthe Grodin, Jean-Charles Guimond, Nashwa Irfan, Tanja Kalajdzic, Stephanie Labelle, Marion Law, Larissa Lefebvre, Conrad Pereira, Vincent Punch, Andrew Raven, Larissa Reid, Fannie St-Gelai, Dionne Saul-Hamilton, Supriya Sharma, Andrew Slot, Melissa Smith, Emma Spreekmeester, Fuhu Wang,

Day 1: 15 November 2016

Welcome and opening remarks (Marion Law)

The Director General of Therapeutics Products Directorate welcomed the scientific advisory panel members. She provided context for the meeting, which was to assist in better informing Canadians about the risks of opioid use. This is in accordance with the five-point action plan put forward by the Minister of Health. She explained the process to be used for the meeting, and once again thanked the panel for their time and for providing advice to Health Canada. She then handed the meeting over to the Chair of the panel.

Chair's address (Jason Busse)

The Chair asked members and observers to introduce themselves. He then confirmed acceptance of the terms of reference of the panel and the draft for the meeting, before leading the panel members in a short verbal declaration of affiliations and interests. No significant financial conflicts of interest were declared. Before the presentations commenced, the Chair briefly reviewed the process to be followed with respect to asking questions of the presenters.

Presentations (Day 1)

1. Scientific Advisory Panel on Opioids (Léo Bouthillier)

The presentation included a summary of the SAP-Opioid's mandate, the Minister's five-point opioid action plan, an overview of existing Health Canada product monographs for some opioid products, and content of examples of current warning stickers and patient information handouts. The presentation concluded by reiterating the questions posed to the panel.

Issues raised by the panel, in questioning the presenter, included, but were not limited to:

- Use of terms such as misuse and abuse, as opposed to more current nomenclature that recognized these issues as a disease (e.g. opioid use disorder) and avoids terms that may stigmatize patients.
- Difference between physical dependence and addiction, and the importance of conveying that long-term opioid use will result in the development of physical dependence.
- Challenges associated with keeping terminology current and consistent in regulations or guidelines.
- Communication of the absolute increase in risks and benefits, clearly and quantitatively, in labelling.
- Utility of decision-aids for patients, when communicating with their health-care provider.
- Effective communication with health care providers, on updates regarding information on drugs.
- Variety and consistency of databases and sources being used to provide information to patients.
- Need for regulatory tools to help communicate health messages to the public.

2. Patient and Family Communication (Sylvia Hyland)

The presentation included summary of the work conducted by the Institute for Safe Medication Pracctices Canada (ISMP Canada) to encourage patients to be more comfortable asking questions to their physicians or pharmacists about their medications. The ISMP handout regarding the use of opioids and an infographic comparing relative potencies of different opioids were also discussed.

Issues raised by the panel, in questioning the presenter, included, but were not limited to:

- Utility and limitations of the morphine equivalents scale when comparing different opioids.
- Messaging to opioid-naïve patients versus patients already engaged in long-term opioid use.
- Limited availability of information on how to safely taper opioids.
- Central sensitization in chronic pain.

3. **Effective Health Product Risk Messaging** (Patricia Carruthers-Czyzewski)

The presentation highlighted plain language principles in health product risk communications to healthcare professionals, patients and consumers.

Issues raised by the panel, in questioning the presenter, included, but were not limited to:

- Importance of language when consulting with, and messaging to, all health professionals.
- General effectiveness of stickers in conveying messages associated with the use of drugs.
- Difficulty of condensing important information into a short handout.

Deliberation on the questions posed (All panel members)

In addition to the above points, the discussion covered other areas, including:

- Which currently used warning stickers are most effective.
- Value of pictograms on stickers for communicating messages.
- Physical limitations of warning sticker use on dispensed medication containers (e.g. how many is too many).
- Variability in definitions of 'misuse'.
- Harms associated with opioids, other than addiction and opioid use disorder.
- Consequences of opioid-induced hyperalgesia.
- Consequences for patients who use the drug as prescribed and benefit from it.
- Need to distinguish between physical dependence and addiction.

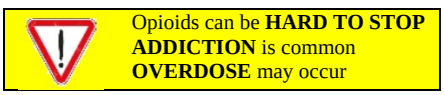
The above list is by no means exhaustive and is intended only to give a sense of the type of issues discussed by the panel.

Final recommendations – Day 1 (All panel members)

(Note: Questions (in italics) posed by Health Canada, precede each set of recommendations)

In line with the Minister of Health's Opioid Action Plan, Health Canada will be mandating standard warning stickers and patient handouts for all dispensed opioids to mitigate the risks of overdose and addiction. While the design and implementation are beyond the scope of this panel, Health Canada is requesting panel input on the ***content*** *of the warning stickers and patient handouts:*

1. *What content should be included in the warning stickers to reflect the risks of overdose and addiction?*



The panel recommended the warning sticker above, to highlight the issues of physical dependence, addiction and overdose. They suggested that the sticker colour be fluorescent yellow or orange, not red and not green. The rationale for not using red is because black writing would be hard to read on a red background and green usually implies something positive. The fluorescent colour was suggested to attract the user's attention.

2. *What key messages should be included in the one to two-page patient handouts to reflect the risks of overdose and addiction?*

The panel's recommendations for the content of a patient handout are as outlined in the following draft:

Opioid Medicines

Information for Patients and Families

- Opioids may be part of a pain treatment plan but are not considered first line management for chronic pain.
- Be sure to use opioids only for the condition for which it was prescribed following the directions of your prescriber.
- If your pain increases or you develop side effects, tell your doctor immediately.

SERIOUS WARNINGS

- **Physical dependence** occurs with daily use of opioids, and can make stopping this medicine difficult. **Symptoms of withdrawal** may occur when the dose is reduced or when opioids are stopped abruptly and may include: diffuse pain, irritability, urge to take the next dose, abdominal cramping, diarrhea, agitation, insomnia, flu-like symptoms. Pain caused by withdrawal can be misinterpreted as on-going benefit from continued use of opioids.
- **Addiction** occurs commonly during regular use and means loss of control over opioid use despite harm.
- **Opioid overdose can lead to death** and is more likely at higher doses.
- **Taking an opioid with alcohol or other sedating drugs** including sleeping pills, anxiety medication, anti-depressants, muscle relaxants, etc., increases the risk of overdose and death.

SIGNS OF OVERDOSE

Signs of overdose include:

- extreme drowsiness
- unable to be woken up by shaking of shoulders or shouting
- slow or unusual (or unusually loud) breathing
- pale and clammy skin

If you suspect an overdose or think you have taken too much opioid medication, get immediate medical help (call 911).

YOUR OPIOIDS MAY BE FATAL TO OTHERS

Store your opioid medication in a secure place to prevent theft, misuse or accidental exposure.

Never give your opioid medication to anyone.

Keep opioid medication out of sight and reach of children and pets.

Return unused or expired opioid medication to the pharmacy for proper disposal.

Your opioid medication should never be thrown into household trash, where children or pets may find it.

OTHER SERIOUS SIDE EFFECTS

- Hyperalgesia - opioids can make pain worse, especially at high doses
- Cognitive function – opioids may cause impairment
- Hormonal disruption - infertility in women, impotence in men
- Severe constipation or bowel obstruction
- Risk of falls, fractures
- Depression
- May cause or worsen sleep apnea
- Babies born to mothers taking opioids may develop life-threatening withdrawal symptoms

This leaflet is a summary and will not tell you everything about this drug.

Always ask your doctor or pharmacist if you have any questions about your opioid medication. For more information, access the online Drug Product Database: https://health-products.canada.ca/dpd-bdpp/index-eng.jsp

Day 2: 16 November 2016

Presentations (Day 2)

4. "High-potency Opioids" Classification for Mandatory Risk Management Plan Requirement (Jiazhen Minnie Dai)

The presentation gave a brief overview of the current opioid crisis in Canada and Health Canada's analysis toward defining 'high-potency opioids'.

Issues raised by the panel, and questions to the presenter, included, but were not limited to,

- Difficulty with the use of morphine equivalent doses and determining conversion factors for some opioids - but agreement from the panel that a system to standardize opioid dose was important.
- Focusing on the drug substance instead of the drug product because the substance is a more stable entity. It would be difficult to update regulations in a timely manner for individual drug products.
- Consideration of other factors in addition to host behavior in defining problems related to opioids.
- Consequences of illicit use by some individuals.
- Consequences for patients who use the medication as prescribed.
- Effect on workload, of requiring post-market surveillance information on a larger number of opioids rather than a restricted number of opioids.

5. Risk Management Plan Requirements and Current Challenges (Tanja Kalajdzic)

The presentation gave an overview of Health Canada's approach to risk management plans, a description of opioid-specific plans reviewed by Health Canada and current regulatory challenges with respect to requiring risk management plans for opioids.

Issues raised by the panel, and questions to the presenter, with respect to developing risk management plans, included, but were not limited to:

- Potential for differences in interpretation of trial results depending on who conducts the trial and interprets the results (e.g. there may be different interests among industry, whose mandate is to maximize profits, and researchers, whose mandate is generally to advance evidence-based care, that may influence reporting of trial results).
- Need for rigorous data from studies conducted by independent academic groups.
- Usefulness of active versus passive surveillance; the latter may seriously underestimate harms.
- Need for standardized education of prescribers, and also for caregivers, on opioid use.

Deliberation on the questions posed (All panel members)

Discussions took place following each presentation. In addition to the points covered after individual presentations, the general discussion also covered a number of issues, such as:

- Need for studies (and discussion of study design) on harms associated with opioid use.
- Variability in availability of data, on major harms, in different Provinces.
- Value of observational studies (e.g. cohort and case control studies) versus cross-sectional studies, when exploring predictors of harm.
- Definition of misuse
- Meaning of 'high potency' opioids in the current context.

The above list is by no means exhaustive and is intended only to give a sense of the type of issues discussed.

Final recommendations - Day 2 (All panel members)

(Note: Questions (in italics) posed by Health Canada, precede each set of recommendations)

Question regarding Classification

> *Does the Panel support Health Canada's proposed approach to classify "high potency" opioids (All full μ-opioid receptor agonist with morphine milligram equivalent (MME) conversion factor equal or greater than 1 by at least one route of administration)?*
>
> *Would the Panel have suggestions on modifications to the approach proposed or alternative options to consider (not limited to those presented in Health Canada's option analysis)?*

The panel recommends use of the term "high *priority* opioids" and not "high potency opioids". Further, the panel endorses use of option #3 as a strategy to classify high priority opioids, with the following caveat: the panel considers all opioids to entail risk, and the focus on opioids that satisfy the criteria of option #3 emphasizes that these opioids are currently implicated in the majority of opioid-related harms in Canada. Opioids that do not fulfil criteria listed in option #3 (e.g. tramadol, codeine) still present risk of opioid-related harms.

Questions regarding Risk Management Plans

> *1) Risk monitoring:*
> *What would be the advice of the Panel on the types of monitoring schemes and post-market studies Health Canada could request from current or future market authorisation holders in order to generate reliable and comprehensive data on the abuse potential of opioids in the post-approval phase in Canada?*

The panel holds that the focus on abuse potential is misplaced, as the terminology may be interpreted as blaming the patient. Studies to detect both risks of, and incidence of, serious but rare adverse drug-related events will need to be observational in design. High quality, existing databases should be used to conduct observational studies to establish the rate of addiction and overdose associated with opioids. Higher quality evidence is likely to come from well-designed, prospective observational studies; however, such studies will require more time and resources. Observational studies (e.g. cohort studies, case-control studies and others) can be undertaken to inform risk factors associated with opioid addiction and opioid overdose; however, risk factors should not be collected at the same time as the outcome of interest. Study protocols should be prepared prior to initiating studies, ideally with input from methodologists and statisticians. The choice of risk factors should be made a priori, and with the anticipated direction of effect to reduce the risk of spurious findings. Factors that have already been established by the literature should be included (e.g. history of mental illness, childhood trauma, current or previous substance use disorder, age). Further, significant associations for risk factors should be presented, when possible, as both relative and absolute effects. The most reliable evidence will emerge from research in which the industry sponsor's role is restricted to review of the protocol and provision of non-binding feedback. Study design, implementation, or interpretation should not be unduly influenced by parties that stand to benefit financially from the results. Post-marketing studies should be designed, conducted, and reported by not-for-profit (academic) organizations.

2) *Risk minimisation:*
   2a) What type of risk minimisation measures could be mandated by Health Canada to minimise the risk associated with opioid use, in order to prevent abuse? For example, in addition to the strengthened labelling such measures could include restrictions to the distribution, training, educational material, continuing medical education (CME), etc.

The panel recommends against a focus on the term "abuse", which implies behaviours rather than outcomes, and instead a focus on opioid-related harms (e.g. overdose, addiction, opioid-related motor vehicle collisions and falls, opioid-induced hyperalgesia). Although the provision of education alone has shown limited impact for changing prescriber behaviours (~1%), it is recommended that Health Canada request manufacturers to provide education regarding both benefits and harms associated with evidence-based opioid prescribing. Manufacturers should be required to adhere to core content approved by Health Canada when developing educational materials. Health Canada should also strongly encourage healthcare providers (*e.g.* physicians, pharmacists, nurse practitioners) to implement decision aids that will developed as part of the 2017 Canadian opioid guidelines during the patient encounter when a prescription for opioids is being considered. The panel further recommends that Health Canada ask manufacturers to provide a patient consent form with clear indications and contraindications to opioid use, as well as a risk factor checklist for health care providers to guide patient-physician interaction regarding the appropriateness of opioid prescribing, weighing both harms and benefits for the individual patient.

Pending release of the 2017 Canadian opioid guidelines, the panel recommends adding the guideline-recommended maximum daily dose of opioids for chronic non-cancer pain to labelling of all opioid products.

2b) How could the effectiveness of risk minimisation measures be evaluated and reported to Health Canada?

The panel noted the limitations of industry-reported evaluation results of risk minimization measures. The number of healthcare providers that complete manufacturer's education program regarding evidence-base opioid prescribing can be captured. Educational programs provided by manufacturers should be periodically monitored for adherence to Health Canada's approved core material. Physicians and patients can be surveyed after implementation of risk mitigation strategies in order to assess self-reported use and satisfaction, and acquire feedback for improvement.

Closing remarks / Adjournment (Chair)

The Chair and Health Canada thanked the members for their participation. The meeting was adjourned**.**

[Note: This record of proceedings was submitted and approved in English by the Chair of the SAP-Opioids.]