PRN Protocols: Applying Pharmacokinetic Principles to Practice; Supporting Individuals with Developmental Disabilities and Mental Health Concerns in Community Settings

Robert King, M.D., FRCP(C),¹ Jan Wilson, RN² & Joan-Ann Atchison²

¹Northeast Mental Health Centre, North Bay, Ontario, Canada
²Assertive Community Treatment Team for Persons Dually Diagnosed, Brockville Mental Health Centre, Brockville, Ontario, Canada

Aggression and self-injurious behavior are frequent impediments to optimizing quality of life in individuals with developmental disabilities and mental health concerns, living in community settings. The safe and efficacious use of Pro Re Nata medication can compliment the development of multimodal support plans to optimize outcome in this context. This article discusses the application of pharmacokinetic principles to the development and revision of these plans.

Keywords: developmental disability, PRN protocols, psychotropic medication, intellectual disability, psychiatric

The Ontario Provincial Government in Canada has recently announced (May 18, 2005) funding for specialized group homes in the province of Ontario to support individuals with developmental disabilities (DD) and challenging behaviors and/or mental health concerns.⁷ Preceding this announcement, in September 2004, the Ministry of Community and Social Services of Ontario announced a five-year plan to close the three remaining institutions in Ontario in which approximately 920 individuals with DD reside. Concurrently the Ministry of Health and Long-Term Care of Ontario continues to promote community-based services while closing long-term psychiatric beds. A recent study in Ontario¹⁵ demonstrated that “as many as 13% of provincial psychiatric hospital (a group of ten formerly Ministry of Health and Long-Term Care administrative facilities, seven of which are now divested to independent boards) users had a dual diagnosis (DD and mental health concern).” Some sites identified as many as 36% of their patients as having a dual diagnosis.¹⁴ Many of these individuals have complex mental health needs and histories of challenging behavior, including extensive self-injury and aggression.¹⁴ The need to develop comprehensive support plans based on proactive principles, combined with contingency planning for crises, to support individuals moving from Ministry of Community and Social Services institutions or Ministry of Health and Long-Term Care hospitals to community settings in Ontario, is well documented.³,⁵,⁸,⁹ Challenging behavior has been the most commonly identified predictor of people’s removal from community programs and precipitant to admission or readmission to institutional or hospital settings.¹⁰ A recent Norwegian study¹⁵ which followed individuals post-discharge shows remarkable stability in psychiatric problems among people who had psychiatric disturbances before being released from institutions.” These authors concluded that “deinstitutionalization has not been shown to solve any problems connected with the mental health of people with intellectual disabilities.” (p.528) An acknowledgment of these challenges has led to calls for the enhancement of community crisis management capacity, with an emphasis on positive behavioral supports, adaptive skill building, and the assessment and treatment of underlying physical and psychiatric disorders amongst individuals with DD living or returning to community settings. Several recent publications have articulated both principles to guide the development of the pro re nata (PRN) prescription of psychotropic medication and have made specific recommendations regarding the use of medication in emergency situations in community settings.¹,¹⁰,¹¹ Zelenski¹⁸ states, “What constitutes an emergency, often associated with violent actions, frequently depends on the juxtaposition of factors relating to the individual and to the environment rather than being intrinsic to the individual with

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DD. (p.11) Kalachnik et al.\textsuperscript{11} have outlined the historical development of legal options and legal precedents established in the United States, which have influenced current guidelines and standards in that country regarding the use of PRN psychotropic medication to support individuals with DD. These authors have established a set of guidelines which offer:

1. Definitions of psychotropic medications.
2. A discussion of potential and appropriate use of these medications.
3. An emphasis on the value of incorporating the use of psychotropic medication into a multidisciplinary plan with specified parameters for use. These parameters include planned alternatives in the event of non-response or adverse reactions, dose levels and ranges, titration plans, response time lines, actions in the event of adverse effects, alternatives in the event of non-response, outcome indicators, and time lines for serial reviews and expected duration of use.

Common errors in the development of PRN utilization guidelines include:

1. Failure to recognize environmental contributions to an individual's challenging behavior.
2. Failure to recognize the underlying presence of a mental illness as a contributing factor to challenging behavior (due to lack of education amongst care providers, inadequate support resources, the attribution of the challenging behavior by care providers to the fact that the individual has a DD (diagnostic overshadowing)),\textsuperscript{17} the attribution of challenging behavior to learned behavior (behavioral overshadowing).
3. Over-diagnosis of psychosis amongst individuals with DD.
4. Utilization of behavioral norms more appropriate for individuals without DD.
5. Assignment of a diagnosis to justify the prescription of a medication (for example, the assignment of a diagnosis of an atypical psychosis to justify treatment with a sedating, traditional, low-potency antipsychotic).
6. Using an either/or dichotomy as opposed to promoting the benefits of synergistic positive effect between medications, behavioral support plans, skill building and habilitative interventions.\textsuperscript{16}

The long term “use of PRN’s” “beyond a few weeks” is cited as a “practice to minimize,” promoting a need to “consider an environmental cause or to review the treatment plan.”\textsuperscript{16} Anecdotally, however, mental health clinicians supporting individuals with DD and mental health concerns in community settings, struggle with the possibility that prescribed psychotropic PRN medication may in fact be underutilized in supporting these individuals. They question whether there are circumstances in which the long-term prescription of PRN medication appears clinically and ethically justifiable. The latter contention is supported by the chronic, recurrent nature of all Axis I DSM-IV\textsuperscript{2} diagnoses, diagnoses often difficult to establish with certainty and precision in individuals with DD. The continued inadequacy of community support resources in many jurisdictions compounds the challenge of establishing DSM-IV-TR diagnoses with confidence. Criscione et al.\textsuperscript{3} have identified characteristics of services, availability of early intervention and preventative services, lack of staff training, the behavior of individual practitioners, and local and national policy as important determinants of admission to hospital (i.e., failure of community placements).

In some clinical situations, a cost/benefit analysis, particularly with respect to issues regarding physical harm to an individual and/or other individuals in his or her environment may well justify the continued use of PRN medication, even in the absence of a confident established diagnosis.\textsuperscript{3} PRN medication utilization, if prescribed in the context of a comprehensive multimodal support plan, can safely and effectively enhance potential impact on quality of life, of regularly prescribed medication and non-medication interventions.

At times, philosophical differences of opinion amongst care providers may also arise, stemming from, in some instances, a lack of knowledge regarding the science of medication utilization (pharmacokinetics). King et al.\textsuperscript{13} have previously described an approach to guide multidisciplinary teams to develop community based PRN programs, utilizing historical and prospective information.

Kalachnik et al.\textsuperscript{11} suggested that overcoming obstacles to the optimal use of PRN medication can be guided by answers to the questions: Are
the right people being treated? and: Is the medication properly monitored and managed? In order for a multidisciplinary team to develop an optimal set of guidelines regarding the utilization of PRN medication, knowledge regarding the pharmacokinetic properties of available medication options is necessary. Pharmacokinetics is the science describing response to exposure to a drug, including factors affecting the drug's absorption, distribution, metabolism and excretion from the body. Understanding these principles assists care providers in answering the following questions:

1. Do we have time to safely utilize a medication at this time, under these circumstances, with available resources, in this environment? (onset of action)

2. What is the expected latency between the provision of a medication and the onset of action?

3. What is the duration of action of a single dose? (dosing interval)

4. Should we anticipate the need for multiple doses in a specific time frame?

5. What is the maximum number of doses which can safely be used in a twenty four hour period?

Drugs from multiple classes, including traditional and atypical antipsychotics, benzodiazepines, mood stabilizers, antidepressants, buspirone, beta blockers and clonidine all have the potential to decrease the intensity and frequency of aggressive behavior and/or self-injurious behavior if utilized as rational components of a holistic support plan. Each PRN medication, regardless of its class, shares the following properties.

1. **Onset of action.** This is the time frame in which efforts to support the individual non-pharmacologically remains critical.

2. **Duration of action.** This property guides physicians in choosing initial dosing intervals.

3. **Therapeutic range.** This range is characterized by:
   a. A **therapeutic threshold** below which the drug has a suboptimal effect.
   b. A **toxic threshold** above which adverse effects increase in the absence of any further positive effect.
   c. A **therapeutic maximum serum concentration** \( (T_{max}) \), the maximally attained serum concentration after a single dose of a PRN medication.

**GRAPH 1**

**GRAPH 1** illustrates these concepts, depicting the theoretical pharmacokinetic time course of a single dose of oral PRN medication.

The subsequent graphs illustrate pharmacokinetic principles important to understand to allow the safe and efficacious use of PRN medication in crises situations. Individuals with DD are sensitive to potential adverse effects of PRN medication and may be at risk of paradoxical disinhibition with benzodiazepines. It is therefore recommended to begin PRN medication at the extreme low end of the theoretic dose range for the specific medication chosen.
GRAPH 2 illustrates the failure to attain a therapeutic serum maximum level of a medication (a level above the therapeutic threshold for a given individual). On serial assessments, in this circumstance, this would be reported by care providers as a lack of an observed sedative therapeutic response to PRN medication. It is therefore critical to include in the PRN protocol, a monitoring system which allows the documentation of a brief description of the critical incident, the time medication was dispensed, the time of response observed, the characteristics of this response. Increasing the initial dose or the route of administration (for example, providing a liquid or intramuscular versus an oral formulation of a prescribed medication) may be appropriate recommendations in this context.

GRAPH 3 illustrates the outcome of the use of an excessive initial dose of a PRN medication resulting in a T_max beyond the serum toxic threshold with resultant observed clinical adverse effects (dysarthria, ataxia, and over-sedation in response to a benzodiazepine; over-sedation and extra-pyramidal adverse effects secondary to an anti-psychotic).

GRAPH 4 illustrates the use of an extended dosing interval (for example, 4 - 6 hours) in the context of a therapeutic initial dose leading to a need to shorten dosing intervals to avoid inter-dose escalation of crisis. This intervention may also be necessary in some individuals who are ultra-rapid metabolizers of prescribed psychotropic PRN medication.

GRAPH 5 illustrates the outcome when the medication has a less than optimal duration of action. The appropriate clinical response would be a decrease in the subsequent dosing intervals. Care providers in this context would likely report an initial, but non-sustained sedative response to prescribed PRN medication with a resultant re-escalation of the intensity of challenging behavior.
Graph 6 depicts a hoped for response to an abrupt, high intensity crisis situation (i.e., a decrease in the intensity of the indexed challenging behaviors, a shortening of the duration of this crisis, and a decrease in likelihood of subsequent crisis occurring later in the day). If historical data suggests the likelihood of similar events in the future, prescribing either higher initial doses of a benzodiazepine or antipsychotic, or drugs from both of these classes in combination, may be indicated.

Graph 7 depicts the time course of a crisis potentially representing a paradoxical response to a prescribed PRN medication. A recent literature review suggests behavioral adverse effects secondary to benzodiazepines occurred in 11.4 to 25% of clinical situations for which data was available in 446 individuals with DD. Care providers would observe an intensification of challenging behavior, over at least several trials with the same medication, within the context of consistently applied non-pharmacological methods of support.

Graph 8 depicts the pharmacological outcome of administering multiple doses of PRN medication, leading to a steady state accumulation of serum mediation levels beyond an individual’s toxic threshold, resulting in clinically observed adverse effects (again including sedation, dysarthria and ataxia in response to a prescribed benzodiazepine and excessive sedative and extra-pyramidal adverse effects when a typical antipsychotic is prescribed). In addition to beginning with low doses of prescribed PRN medications to minimize this outcome, it is important to include a maximum number of PRN doses to be dispensed in a 24 hour period.
CONCLUSION

A comprehensive PRN protocol or crisis support plan is critical in maintaining the right of individuals with DD and mental health concerns and/or seriously challenging behaviors, to live in safety and harmony in community settings which optimize their quality of life. Basing treatment recommendations to community support networks, on sound pharmacokinetic principles, will optimize the achievement of these goals. A commitment from an interdisciplinary team to regularly review objective data depicting the circumstances in which PRN medication is used, in the context of a comprehensive biopsychosocial plan, will inform prescribing physicians regarding drug type, dose, formulation, dosing interval, and 24 hour total amounts of medication necessary to optimize this process. Not infrequently this process highlights other aspects (behavioral and habilitative) of a PRN plan in need of inclusion or refinement in the crisis support plan. In addition, an overall reduction in the utilization of medication as individual skills develop often ensues.

REFERENCES


CORRESPONDENCE: Dr. Robert King, Northeast Mental Health Centre, Hwy. 11N, PO Box 3010, North Bay, ON, Canada P1B 8L1; tel.: 705-494-3197; email: RKing@nemhc.on.ca.