A common road map for rational clinical and policy decisionmaking: application of the MCDA-based EVIDEM framework to growth hormone in patients with Prader-Willi syndrome

Michèle Tony MSc,[1,2] Mireille M. Goetghebeur PhD,[2,3,4] Hanane Khoury PhD,[3] Monika Wagner PhD,[3] Cheri L. Deal PhD, MD[4,5]

Renaldo Battista MD, ScD,[1,4]

[1]Health Administration, Medical Faculty, University of Montreal, Montréal, Québec, Canada; [2]EVIDEM Collaboration and [3]BioMedCom Consultants inc., Dorval, Québec, Canada; [4]Research Center, CHU-Sainte-Justine and [5]Department of Pediatrics, Medical Faculty, University of Montreal, Montréal, Québec, Canada

Background & Objective

- Healthcare decisionmaking is a complex process that requires consideration of a wide range of scientific and contextual criteria and inherently involves value judgments.[1]
- At the policy level, this process demands transparency, consistency, and accountability to be perceived as legitimate and to increase the likelihood of making good decisions.[2,3] At the clinical level, development of recommendations to guide clinical practice also requires consideration of a broad range of aspects to ensure optimal care[4,5] and social responsibility.
- The EVIDEM framework is an MCDA-based adaptable framework to synthesize and consider evidence for each decision criterion.[6,7] It provides a consistent structure to organize evidence and facilitate both clinical and policy making by supporting respectively clinical practice guidelines (CPGs) development and health technology assessment (HTA) and appraisal.
- Prader-Willi syndrome (PWS) is a rare and complex multisystem disorder, with serious long-term consequences. Use and coverage of growth hormone (GH) in patients with PWS vary widely internationally and there is a need to clarify its benefits.
- Objective: Develop a comprehensive web-based validated by-criterion HTA report to support and streamline clinical and policy decisionmaking

Methodology

- An extensive literature review was performed to identify available evidence on GH for PWS for each criterion of the framework covering disease impact, therapeutic context, treatment outcomes (efficacy/effectiveness, safety, patient-reported outcomes), type of benefits and economic impact (MCDA Core Model) as well as ethical and contextual considerations (Contextual Tool).
- Given the complexity of the efficacy outcomes measures reported, the efficacy criterion was subdivided into sub-criteria for each type of outcome measured including growth, body composition, exercise tolerance, metabolic effects, bone health, cardiovascular health, psychomotor development and behavioral outcomes.
- Data was organized in evidence tables and synthesized; level and strength of evidence were assessed using respectively the Centre for Evidence-Based Medicine (CEBM) levels of evidence[8] and EVIDEM data quality assessment instruments.
- To support deliberations for CPGs development and policy making, the framework was used to elicit questions and an interactive web information system was developed to facilitate the processes.

Key Steps for Development of Clinical and Policy Recommendations Using EVIDEM

Results

- Based on the analysis of the literature and feedback from experts, questions reflecting current issues in management of patients PWS were developed and organized using the adapted EVIDEM framework (Intervention & Overview, MCDA Core Model and Contextual Tool).
- This framework structure and questions identified will be used sequentially to:
  1. Structure a consensus workshop and assign questions to CPGs working groups to develop CPGs guidelines.
  2. Structure deliberations of a pan-Canadian taskforce to examine the conditions for successful implementation (obstacles and facilitating factors) of evidence-based CPGs.

Clinical Aspects

Indication:
1. Do patients with PWS need GH testing: In infancy? In childhood? In adulthood?
2. What baseline evaluations need to be performed before GH treatment?

Intervention duration:
3. For how long should GH therapy be pursued?

Administration/Description:
4. What clinical lab tests or imaging studies need to be done to monitor treatment?
5. What doses should be used for GH therapy: In infants? In children and adolescents? In adults?
6. Is there an optimal level of circulating IGF-I to obtain with GH treatment?
7. Should GH dose be titrated to IGF-I, and if so, at what frequency?
8. What is the frequency of follow-up visits necessary to adequately monitor GH therapy?

Comparator(s):
9. What other therapies/interventions have been tried in PWS?

MCDA Core Model

Decision Criteria	Proposed questions
Disease impact	
D1 - Disease severity	10. What is the frequency of the various genetic subtypes among various populations? 11. How has evolution of our genetic testing methodology changed genetic subtype frequency? 12. Are all patients with PWS equally GH deficient? 13. Are there genotype-phenotype correlations relevant to specific to clinical outcome measures targeted with GH therapy? Other correlations? 14. What are the important co-morbidities that need to be considered when considering GH therapy? 15. What is the life expectancy of PWS subjects? 16. What are the major causes of death in PWS subjects?
D2 - Size of population	17. What is the birth incidence/prevalence of PWS?
Therapeutic context of intervention	
C1 - Clinical guidelines	18. Why are physicians divided in their belief about the benefits of GH therapy?
C2 - Comparative interventions limitations *(unmet needs)*	19. For each of the other therapies/interventions tried in PWS, what were: The specific outcomes? The efficacy per outcome? The safety/tolerability of the therapy/intervention? 20. What specific therapies/interventions have been tried concomitant to GH therapy? 21. What are the nutritional recommendations for: Infants with PWS? Children with PWS? Adolescents with PWS? Adults with PWS?
Intervention outcomes	
I1 - Improvement of efficacy/ effectiveness	22. What are the most important clinical outcome priorities when initiating GH therapy in subjects with PWS: In infancy? In childhood? In adolescence? In Adulthood? 23. What is the best way to measure GH effectiveness on: a. Growth; b. Body composition; c. Motor development (infants and children); d. Neurological status; e. Physical activity; f. Muscle strength; g. Metabolic benefits; h. Resting energy expenditure; i. Cardiovascular status; j. Bone health; k. QoL (specifically in intellectually-disabled individuals) 24. What is the impact of other hormonal deficiencies on GH treatment? 25. Does response to GH vary by: a. age at start of treatment; b. dose; c. body composition at start; d. degree of dietary control; e. level of physical activity
I2 - Improvement of safety & tolerability	26. What are the major serious adverse events of GH treatment of PWS subjects? 27. What is the evidence that GH treatment in PWS increases the risk of: a. Sleep apnea; b. Sudden death; c. Scoliosis; d. Diabetes; e. Intracranial hypertension; f. Epilepsy; g. Slipped capital femoral epiphyses; h. Oedema; i. Breast tenderness/enlargement; j. Risk of infection; k. Joint pain; l. Neoplasia; m. Arterial Hypertension; n. Strole/intra-cranial bleeding 28. What is the tolerability of GH: In published clinical trials (dropouts rate)? In patient-reported data? In phase 4 trials? In smaller observational studies? 29. What are the main reasons given for patient withdrawal from clinical trials of GH in PWS?
I3 – Improvement of patient reported outcomes	30. What are the most significant benefits reported by patients and/or parents after GH treatment?

MCDA Core Model (continued)

Decision Criteria	Proposed Questions
Type of benefit	
T1 - Public health interest *(e.g., prevention, risk reduction)*	31. Is there any risk reduction associated with GH treatment in patients with PWS?
T2 - Type of medical service *(e.g., cure, symptom relief)*	32. What are the least important, but significant, clinical outcomes to GH therapy? 33. What known GH effects have not been adequately studied in PWS?
Quality/uncertainty of evidence	
Q2 - Completeness and consistency of reporting evidence Q3 - Relevance and validity of evidence	34. What are the confounding variables that are difficult to control in PWS GH clinical trials? 35. What is the best way to report efficacy data according to current recommendations, and why? 36. Is there a place for a therapeutic trial of GH, and if so, how long before assessing GH effectiveness? 37. When sources of potential study bias are considered (adequate randomisation and blinding of patients and health professionals, adequate description of withdrawals and dropouts, provision of intention-to-treat analysis), what proportion of the clinical trials have a high risk of bias, ie, one or more of the previous criteria not met)? 38. What questions with regards to GH use in PWS require further study? 39. What are the major research areas with regards to PWS that need to be addressed beyond issues of GH use?

Resource Allocation and Ethical Aspects

Overview

Economic burden of illness:
40. What are the major sources of healthcare costs related to the care of patients with PWS?
41. What are the major costs of treating morbid obesity?
42. What are the major costs of treating diabetes?

MCDA Core Model (continued)

Decision Criteria	Proposed Questions
Economics of intervention	
E1 - Budget impact on health plan *(cost of intervention)*	43. What is the cost of GH treatment in patients with PWS? 44. What is the budget impact at the country level?
E2 - Cost-effectiveness of intervention	45. What is the cost-effectiveness of GH treatment in patients with PWS?
E3 - Impact on other spending *(e.g., hospitalization, disability)*	46. What are the economic consequences (beyond drug cost) of GH treatment in patients with PWS?

Contextual Tool

Decision Criteria	Proposed Questions
Ethical criteria	
Et1 - **Utility** - Goals of healthcare	47. Is the use of GH in patients with PWS aligned with the mission and scope of healthcare systems?
Et2 - **Efficiency** - Opportunity costs & affordability	48. How do we prioritize resources for PWS care, and how does GH fit into this?
Et3 - **Fairness** - Population priority & access	49. Is access to GH therapy available to all PWS patients, and if not, why? 50. Are there issues of fairness in withholding GH treatment, or in targeting specific sub-populations of PWS subjects for GH therapy?
Overall context	
O1 - System capacity & appropriate use of intervention	51. How do we organize the comprehensive care of the PWS patient, to optimize GH treatment and particularly to decrease/prevent potential side effects? 52. What are the evidence-based steps that are needed to harmonize care of patients with PWS?
O2 - Stakeholder pressures/ barriers	53. Are there any pressures/barriers for the use of GH in patients with PWS?
O3 - Political/ historical context	54. Are there any specific political/historical context impacting the use of GH in patients with PWS?

Collaborative Web Site

- A collaborative web site was built to facilitate the process including:
  - Access to evidence and questions structured in a consistent systematic manner
  - Interactive online validation by international experts of: synthesized data; quality assessments of evidence; and questions
  - Involvement of all stakeholders prior to the workshops
- To facilitate knowledge transfer, validated synthesized data on GH for PWS, CPGs and taskforce recommendations, and the process to develop them, will be made publicly available under a Creative Common license.[9]

Discussion and Conclusion

- Questions elicitation and organization was facilitated by the EVIDEM framework, providing a pragmatic means to ensure systematic consideration of evidence for a wide range of criteria and associated issues.
- By clearly revealing current knowledge and gaps, the framework is expected tofacilitate developing evidence-based CPGs and policy recommendations as well as identifying research needed for continued improvement of management of patient with PWS.
- This comprehensive by-criteria approach provides a common road map to streamline clinical and policy decisionmaking to optimize patient health, resource allocation and healthcare system sustainability.
- The ultimate goal is to bridge the gap between researchers, HTA, policy decisionmaking, clinical practice and patient concerns.

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