Supplementary Information 1 – PRIMSA reporting guidelines

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4-5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5, Supplementary Information 2
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary Information 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Supplementary Information 2
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Supplementary Information 2
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Supplementary Information 2
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Supplementary Information 2
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Supplementary Information 2
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	N/A
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	N/A
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	N/A
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	N/A
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Supplementary Information 3

Section and Topic	Item #	Checklist item	Location where item is reported
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	N/A
Study characteristics	17	Cite each included study and present its characteristics.	5-7, Table 1 and 2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplementary info 4
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	N/A
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	N/A
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	7-8, Supplementary Information 5
	23b	Discuss any limitations of the evidence included in the review.	7-8
	23c	Discuss any limitations of the review processes used.	7-8
	23d	Discuss implications of the results for practice, policy, and future research.	8
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	2,5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	1,9
Competing interests	26	Declare any competing interests of review authors.	1,9
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A

Supplementary Information 2 – Details regarding inclusion criteria and data extraction

Complete search strings are listed below:

SCOPUS

TITLE-ABS-KEY ((valpro* OR epilim OR dyzantil OR epival) AND (subcut* OR hypoderm*) AND (palliat* OR end-of-life OR hospice OR comfort OR terminal OR symptomatic OR supportive))

EMBASE

((valpro* or epilim or Dyzantil or epival) and (subcut* or hypoderm*) and (palliat* or end-of-life or hospice or comfort or terminal or symptomatic or supportive)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]

PubMed

("valpro*"[All Fields] OR ("epilim"[Supplementary Concept] OR "epilim"[All Fields] OR "epilim"[All Fields]) OR "epival"[All Fields]) AND ("subcut*"[All Fields] OR "hypoderm*"[All Fields]) AND ("palliat*"[All Fields] OR ("death"[MeSH Terms] OR "death"[All Fields] OR ("end"[All Fields] AND "life"[All Fields]) OR "end of life"[All Fields]) OR ("hospice s"[All Fields] OR "hospices"[MeSH Terms] OR "hospices"[All Fields] OR "hospice"[All Fields] OR "hospice care"[MeSH Terms] OR ("hospice"[All Fields] AND "care"[All Fields]) OR "hospice care"[All Fields]) OR ("comfort"[All Fields] OR "comfortability"[All Fields] OR "comfortable"[All Fields] OR "comfortableness"[All Fields] OR "comfortably"[All Fields] OR "comforted"[All Fields] OR "comforter"[All Fields] OR

"comforters"[All Fields] OR "comforting"[All Fields] OR "comforts"[All Fields]) OR ("terminal"[All Fields] OR "terminal s"[All Fields] OR "terminally"[All Fields] OR "terminals"[All Fields] OR "terminate"[All Fields] OR "terminated"[All Fields] OR "terminates"[All Fields] OR "terminating"[All Fields] OR "termination"[All Fields] OR "terminations"[All Fields] OR "terminator"[All Fields] OR "terminators"[All Fields]) OR ("symptomatic"[All Fields] OR "symptomatically"[All Fields] OR "symptomatics"[All Fields]) OR ("support"[All Fields] OR "support s"[All Fields] OR "supported"[All Fields] OR "supporter"[All Fields] OR "supporter s"[All Fields] OR "supporters"[All Fields] OR "supporting"[All Fields] OR "supportive"[All Fields] OR "supportiveness"[All Fields] OR "supports"[All Fields])) Translations epilim: "Epilim"[Supplementary Concept] OR "Epilim"[All Fields] OR "epilim"[All Fields] end-of-life: "death"[MeSH Terms] OR "death"[All Fields] OR ("end"[All Fields] AND "life"[All Fields]) OR "end of life"[All Fields] hospice: "hospice's"[All Fields] OR "hospices"[MeSH Terms] OR "hospices"[All Fields] OR "hospice"[All Fields] OR "hospice care"[MeSH Terms] OR ("hospice"[All Fields] AND "care"[All Fields]) OR "hospice care"[All Fields] comfort: "comfort"[All Fields] OR "comfortability"[All Fields] OR "comfortable"[All Fields] OR "comfortableness"[All Fields] OR "comfortably"[All Fields] OR "comforted"[All Fields] OR "comforter"[All Fields] OR "comforters"[All Fields] OR "comforting"[All Fields] OR "comforts"[All Fields] terminal: "terminal"[All Fields] OR "terminal's"[All Fields] OR "terminally"[All Fields] OR "terminals"[All Fields] OR "terminate"[All Fields] OR "terminated"[All Fields] OR "terminates"[All Fields] OR "terminating"[All Fields] OR "termination"[All Fields] OR "terminations"[All Fields] OR "terminator"[All Fields] OR "terminators"[All Fields] symptomatic: "symptomatic"[All Fields] OR "symptomatically"[All Fields] OR "symptomatics"[All Fields] supportive: "support"[All Fields] OR "support's"[All Fields] OR "supported"[All Fields] OR "supporter"[All Fields] OR "supporter's"[All Fields] OR

"supporters"[All Fields] OR "supporting"[All Fields] OR "supportive"[All Fields] OR "supportiveness"[All Fields] OR "supports"[All Fields] Warnings (valpro* OR epilim OR Dyzantil OR epival) AND (subcut* OR hypoderm*) AND (palliat* OR end-of-life OR hospice OR comfort OR terminal OR symptomatic OR supportive) Term not found: Dyzantil
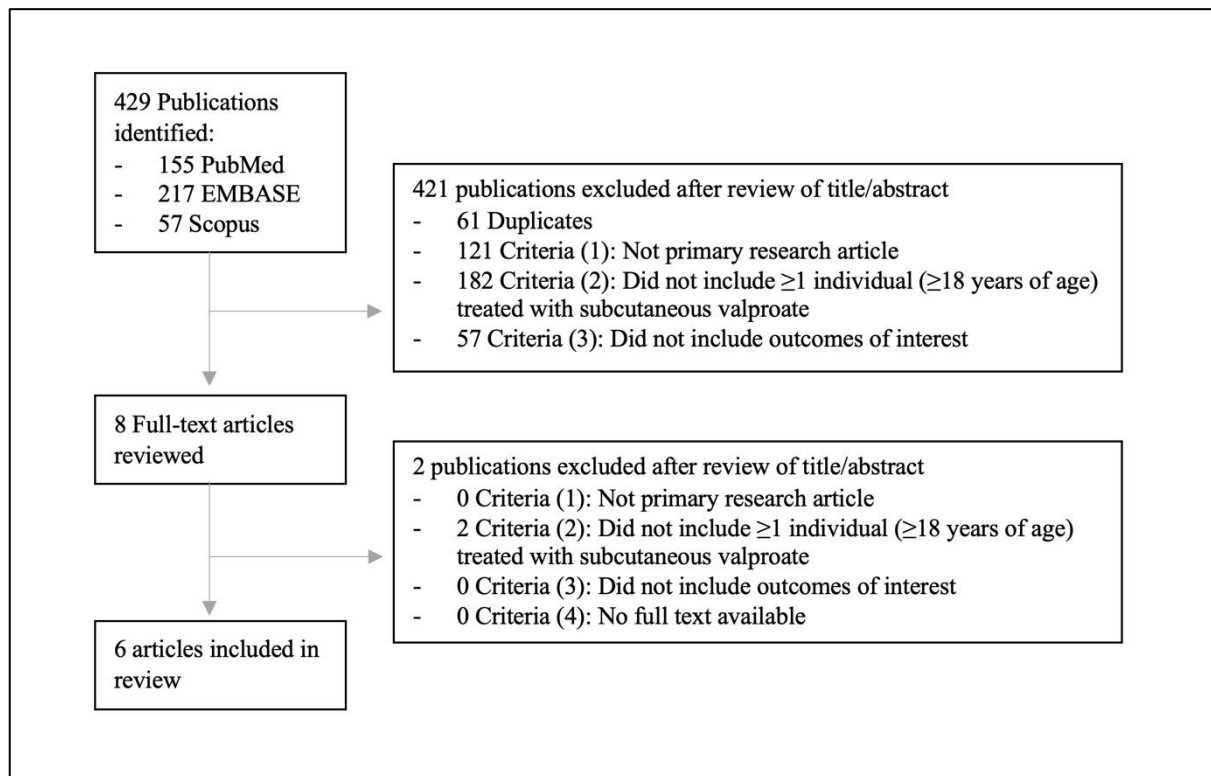
Included articles had their reference lists searched for other studies that fulfilled the inclusion criteria. Evaluation in duplicate was performed to determine whether studies returned by the search met inclusion criteria. Eligibility determination was first conducted based on titles and abstracts using a standardised form. Those that were considered likely to fulfil inclusion criteria, or for which eligibility could not be determined, were reviewed in full-text. The inclusion criteria applied were: (1) Primary peer reviewed publication (including posters, letters and case reports); (2) included ≥1 individual (≥18 years of age) treated with subcutaneous valproate; (3) presented data on outcomes of interest (either efficacy of subcutaneous valproate for symptoms in the setting of palliative care, or tolerability of subcutaneous valproate; and (4) full-text available. All eligibility determination was conducted in duplicate (S.T., J.S., C.T., S.E., S.B.), and instances of disagreement were resolved through discussion with a third reviewer. The Johanna Briggs Institute Critical Appraisal Checklists were used for risk of bias analysis according to study design This evaluation was also conducted in duplicate.

Data extraction and analysis

A standardised form was used to conduct data extraction. Data collected included patient factors (age, gender, comorbidities, and valproate indicate), valproate use (dose, dosing

regimen, and duration of treatment), effectiveness (as reported for each individual indication), and adverse effects (nature and frequency).

Supplementary Information 3 - Study selection

429 Publications identified:
- 155 PubMed
- 217 EMBASE
- 57 Scopus

421 publications excluded after review of title/abstract
- 61 Duplicates
- 121 Criteria (1): Not primary research article
- 182 Criteria (2): Did not include ≥1 individual (≥18 years of age) treated with subcutaneous valproate
- 57 Criteria (3): Did not include outcomes of interest

8 Full-text articles reviewed

2 publications excluded after review of title/abstract
- 0 Criteria (1): Not primary research article
- 2 Criteria (2): Did not include ≥1 individual (≥18 years of age) treated with subcutaneous valproate
- 0 Criteria (3): Did not include outcomes of interest
- 0 Criteria (4): No full text available

6 articles included in review

Supplementary Information 4 – Risk of bias of included studies

Case series

	Cran et al. 2018	O'Connor et al. 2017	Davis et al. 2018	Kondasinghe et al. 2014
Were there clear criteria for inclusion in the case series?	Yes	Yes	Yes	Yes
Was the condition measured in a standard, reliable way for all participants included in the case series?	Unclear	Unclear	Unclear	Yes
Were valid methods used for identification of the condition for all participants included in the case series?	Unclear	Unclear	Unclear	Unclear
Did the case series have consecutive inclusion of participants?	Yes	Unclear	Yes	Yes
Did the case series have complete inclusion of participants?	Yes	Unclear	Yes	Yes
Was there clear reporting of the demographics of the participants in the study?	No	Yes	No	No
Was there clear reporting of clinical information of the participants?	Yes	Yes	Yes	Yes
Were the outcomes or follow up results of cases clearly reported?	Yes	Yes	Yes	Yes
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	No	No	No	No
Was statistical analysis appropriate?	Yes	Yes	Yes	Yes

Cross-sectional study

	Pouchoulin et al. 2014
Were the criteria for inclusion in the sample clearly defined?	No
Were the study subjects and the setting described in detail?	No
Was the exposure measured in a valid and reliable way?	Unclear
Were objective, standard criteria used for measurement of the condition?	Unclear
Were confounding factors identified?	No
Were strategies to deal with confounding factors stated?	Not applicable
Were the outcomes measured in a valid and reliable way?	Unclear
Was appropriate statistical analysis used?	Yes

Supplementary information 5: Practical considerations regarding subcutaneous valproate administration

There are multiple possible challenges that may arise in the palliative management of seizures, including people with a pre-existing antiseizure medication regimen who change deteriorate, or fluctuate with respect to oral intake. One of the potential advantages of having the option of using sodium valproate subcutaneously may be in individuals who were previously on the medication orally, and their seizures were well controlled, but then lose their ability to take oral medications during the palliative course. An additional benefit with the use of a subcutaneous route of administration for antiepileptics is the longevity of the administration site. The subcutaneous cannula can remain in place for up to a week, with policies differing between health institutions.

The doses of valproate in the identified studies varied substantially. This variability is in keeping with clinical experience with oral valproate dosing for different indications.[1] The lowest described effective dose was 400mg/24-hours with the maximum dose being 2500mg/24-hours. With respect to the rate of uptitration, Davis described uptitration occurring in increments no larger than 300mg/24-hours. [2] See below table for summary of subcutaneous sodium valproate dosing considerations.

Summary of subcutaneous sodium valproate dosing considerations

Factor	Evidence
Indications	Studies have described successful use for seizure control and neuropathic pain
Dose conversion	Studies have described converting intravenous : oral : subcutaneous sodium valproate doses as 1:1:1
Concentration	One study reported concentrations varying from 20mg/mL to 50mg/mL.
Dilutant	One study described using 0.9% saline or water for injections.
Dose range	Studies have described an effective range of doses from 400mg/24-hours to 2500mg/24-hours
Uptitration	One study has described a rate of uptitration not exceeding 300mg/24-hour increments

Adverse effects	In the available studies, the only adverse effect described has been a single local site reaction that resolved.
Other considerations	Considerations relevant to the prescribing of other routes of sodium valproate are likely still relevant to subcutaneous sodium valproate (e.g., potential for hyperammonemic encephalopathy)

It should be noted that in the included studies, estimations of subcutaneous doses were made based on biological plausibility. For example, Kondasinghe and O'Connor describe using oral to subcutaneous conversion ratios of 1:1.[3, 4] These conversions are supported by the known high bioavailability of sodium valproate.[5] Similar conversions have previously been made when estimating subcutaneous levetiracetam doses, which may also have a similar role when used subcutaneously in the palliative care setting.[6] Additionally, in multiple studies included in this review, patients were receiving more than one antiseizure medication, including combinations of subcutaneous levetiracetam and subcutaneous sodium valproate.[4]

References

1.   Rahman M and Nguyen H. Valproic acid. *StatPearls*. Treasure Island (FL): StatPearls Publishing, 2020.

2.   Davis C, Crispin H, Marshallsay C, Haig S, Pennell S and Jenks A. Sodium valproate subcutaneous infusion; a valuable adjunct in the management of neuropathic pain in palliative patients. *BMJ Support Palliat Care*. 2018; 8(Suppl 1): A48.

3.   O'Connor N, Hayden C and O'Leary N. Sodium valproate as a continuous subcutaneous infusion: a case series. *J Pain Symptom Manage*. 2017; 54(2): e1-e2.

4.   Kondasinghe JS, Look ML, Moffat P and Bradley K. Subcutaneous levetiracetam and sodium valproate use in palliative care patients. *J Pain Palliat Care Pharmacother*. 2022; 36(4): 228-32.

5.   Johannessen CU and Johannessen SI. Valproate: past, present, and future. *CNS Drug Rev*. 2003; 9(2): 199-216.

6.   Remi C, Lorenzl S, Vyhnalek B, Rastorfer K and Feddersen B. Continuous subcutaneous use of levetiracetam: a retrospective review of tolerability and clinical effects. *J Pain Palliat Care Pharmacother*. 2014; 28(4): 371-7.