

American Clinicians Academy on Medical Aid in Dying

**Adding Phenobarbital to the D-DMA and DDMA
Medication Protocols for Medical Aid in Dying**

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Key:

DDMP2: Digoxin 50 mg, Diazepam 1 gm, Morphine 15 gm, Propranolol 2 gm.

D-DMP2: As above, but digoxin is given separately, 30 minutes before the other medications.

DDMA: Digoxin 100 mg, Diazepam 1 gm, Morphine 15 gm, Amitriptyline 8 gm.

D-DMA: As above, but digoxin is given separately, 30 minutes before the other medications.

DDMAPh: Digoxin 100 mg, Diazepam 1 gm, Morphine 15 gm, Amitriptyline 8gm, Phenobarbital 5 gm.

D-DMAPh: As above, but digoxin is given separately, 30 minutes before the other medications.

ABSTRACT

Background: Since the beginnings of U.S. medical aid in dying in 1997,¹ there has been a need to refine and improve aid-in-dying pharmacology – in efficacy, reliability, time-to-sleep, time-to-death, patient tolerance, simplicity, cost, and availability. This has led to modifications from the originally prescribed secobarbital² to compounded multi-medication protocols. D-DMA or DDMA are now commonly used in all aid-in-dying states.

Hypothesis and Purpose: Phenobarbital is a barbiturate/sedative with gastric absorption and brain GABA-A³ receptor activity. This study presents early data to clarify if adding phenobarbital to DDMA and D-DMA improves the time to sleep and time to death for aid-in-dying patients.

Methods: Physicians from California, Washington, Oregon, New Jersey, and Colorado with active medical-aid-in-dying practices submitted data on patients who received the modified medication regimen: 5 grams of phenobarbital powder added to the presently-used D-DMA or DDMA protocols, forming, respectively, D-DMAPh and DDMAPh. Data was received for 52 patients. Results were compared with D-DMA/DDMA patient data previously compiled by Washington, Oregon, and California aid-in-dying organizations.⁴

Results Summary: Adding 5 grams of phenobarbital to the presently recommended aid-in-dying protocols showed a decrease in average time to death, from 1.5 to 1.2 hours. More importantly, the upper range of times to death also decreased. No additional complications or disadvantages of the phenobarbital protocol were reported.

Conclusions: From this preliminary data report, the authors recommend that D-DMAPh and DDMAPh be used as a standard protocol for medical aid in dying. D-DMA and DDMA remain acceptable options. If ongoing data collection and analysis support the superior results of the phenobarbital-containing regimens, they may become the first-line protocols for all aid-in-dying patients.

DETAILED PRESENTATION

Research rationale:

Research and data collection concerning the pharmacology of medical aid in dying in the U.S. has been complicated by a distinct lack of participation in the search for better drug regimens by the traditional medical research organizations (universities, clinical research centers, and pharmaceutical companies). This may be attributed to medical, religious and political stigma about aid in dying itself. Few, if any, medical organizations are willing to expose themselves to publicity that they are studying methods of ending patients' lives. Additionally, there is little money to be made by pharmaceutical companies in studying these non-lucrative, off-patent drugs.

“Orphaned medications” are defined by the FDA⁵ as medications for rare diseases that would not be studied and produced by drug companies because of the tiny market. The Orphan Drug Act⁶ was established to remedy this deficit by financially incentivizing smaller companies to produce these medications. However, there is no similar incentive for dealing with “orphaned research.” The authors believe that orphaned research applies to medical aid in dying. Investigations into the best medication options available should not be delayed because of the associated stigma or lack of financial incentive. 22% of Americans are currently eligible to legally request aid in dying, and deserve to have efficient, cost-effective medications available. At this point, no traditional research institution is working to orchestrate such studies. As a result, data collection and analysis are left in the hands of the physicians who treat these patients.

The authors contend that data collection is not considered human experimentation, since the drugs prescribed for aid-in-dying patients are already widely used globally. Because these FDA-approved medications are used in the new context of aid in dying, and at different dosages, these prescriptions fit into the ethically and legally accepted realm of [off-label prescribing](#).⁷

Additionally, the usual approval of aid-in-dying investigations by Institutional Review Boards is also hampered by the lack of involvement of traditional research organizations. The authors and the Academy⁸ strongly believe in the ethical imperative of working with Institutional Review Boards whenever possible. To date, Institutional Review Board review has not been achieved due to myriad obstacles.

Given all of the above, the Academy, along with multiple individuals and support organizations in aid-in-dying states, has taken a leading role in working to improve aid-in-dying pharmacology by collecting data to develop best practices in the field. Without such investigations, all

clinicians legally practicing medical aid in dying would be working with blinders on, lacking patient data on which to base their prescription decisions. This preliminary study of phenobarbital-containing aid-in-dying regimens also introduces the Academy's data collection role and system, which is essential to the continued comprehensive assessment of this new medication regimen.

Methodology:

The newly established American Clinicians Academy on Medical Aid in Dying⁹ collected data submitted by experienced aid-in-dying physicians in California, Washington, Oregon, New Jersey, and Colorado.

All participating physicians agreed to prescribe their choice of the following drug regimens:

- DDMAPh: Digoxin 100 mg, Diazepam 1 gm, Morphine 15 gm, Amitriptyline 8 gm, Phenobarbital 5 gm.
- D-DMAPh: The same dosages as above, but with digoxin self-administered separately 30 minutes before the other medications.

The information was submitted for collection through the Data Filing web page of the Academy.¹⁰ The collected data did not contain any patient-identifying information, and all reports contained only aggregated, anonymous data to further protect patient confidentiality. Data analysis from these reports was compared with similar analyses of D-DMA/DDMA data collected by Washington, Oregon, and California support organizations.¹¹

Pharmacist involvement in preparation of the study drug regimens: D-DMAPh or DDMAPh mixtures were provided by the same experienced compounding pharmacists routinely used to prepare D-DMA and DDMA.

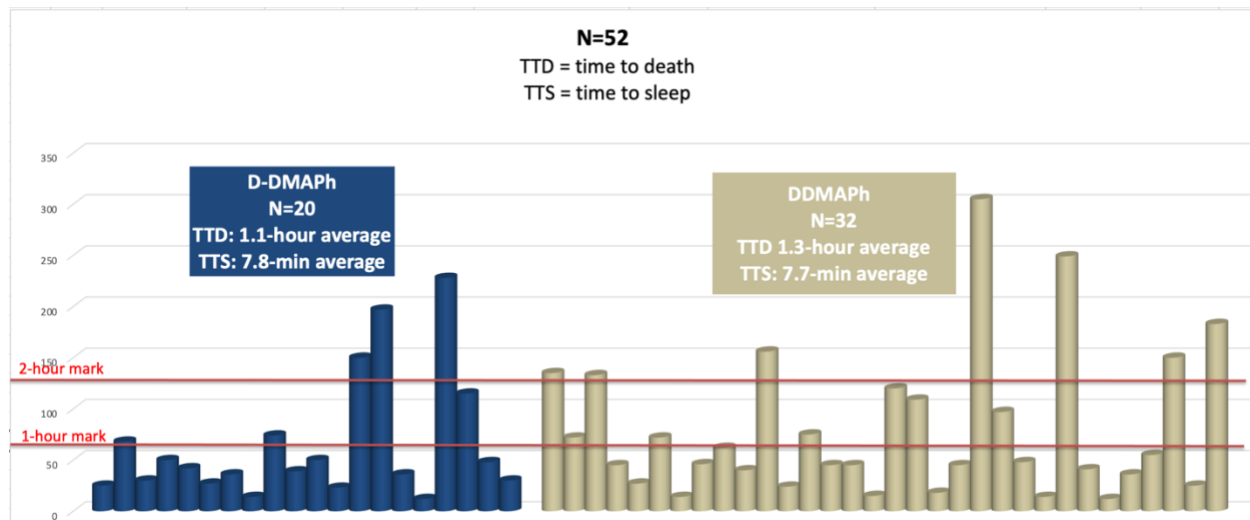
Phenobarbital, a readily available, compoundable powder, did not significantly increase the volume or viscosity of the mixed medications, and did not alter the taste or swallowability of these medications. Adding 5 gm of phenobarbital did not significantly increase the cost of the drug regimen, with most pharmacists wrapping the approximately \$15 increase into the existing price (approximately \$750-800). All medications were dispensed in powdered form.

On the day of death, medications were mixed with liquid at the patients' locations, typically their homes, using the same methods and diluents used for D-DMA/DDMA. Medications were commonly mixed by a trained volunteer or a physician or nurse in attendance, but, especially during these times of COVID restrictions, were also mixed by patients or supportive lay persons. Medications were self-administered by the patients, either orally or through a feeding or rectal tube.

Antiemetics were given to all oral-ingesters an hour before drinking the life-ending medications, as per established aid-in-dying protocol.

Data Analysis:

Patients' Time to Death for Phenobarbital Protocols (D-DMAPh/DDMAPh)



A total of 52 phenobarbital protocol aid-in-dying deaths were reported to the Academy. 20 patients self-administered D-DMAPh and 32 patients self-administered DDMAPh.

Phenobarbital Protocols (D-DMAPh/DDMAPh) vs. Most Commonly Used Non-Phenobarbital Protocols (D-DMA/DDMA)

Time to Sleep and Time to Death

Medication	N	Average time to sleep (mins)	Average time to death (hours)
D-DMAPh/DDMAPh	52	7.8	1.2
D-DMA/DDMA	255	5.8	1.5

Time to Death: Average time to death with the phenobarbital-containing regimens was 1.2 hours, 20% faster than the average time to death with the regimens without phenobarbital.

Time to Sleep: Average time to sleep of the phenobarbital-containing regimen was 7.8 minutes, an increase over the 5.8-minute non-phenobarbital average time to sleep.

**Maximum Time to Death
Phenobarbital vs. Non-Phenobarbital Protocols**

Medication protocol	N	Maximum time to death (hours)
No Phenobarbital		
All	255	12.4
D-DMA	113	6.0
DDMA	141	12.4
With Phenobarbital		
All	52	5.1
D-DMA _{Ph}	20	3.8
DDMA _{Ph}	32	5.1

Maximum time to death: The clear improvement when the phenobarbital-containing regimens were used is reflected in the significant decrease in the maximum time to death, compared to the non-phenobarbital regimens (12.4 hours to 5.1 hours).

**Phenobarbital protocols
Early Digoxin vs. Merged Digoxin**

Protocol	N	Average time to death (hours)	Max time to death (hours)	% deaths < 2 hours
All	52	1.2	5.1	81%
D-DMA _{Ph} (5gm)	20	1.1	3.8	85%
DDMA _{Ph} (5gm)	32	1.3	5.1	78%

Early digoxin vs. merged digoxin: As has been true in prior aid-in-dying studies, average time to death with the use of “early digoxin,” that is, self-administering the digoxin 30 minutes before the other medications, was slightly shorter than when all the powders were ingested at the same time (“merged digoxin”): 1.1 hours for D-DMA_{Ph} vs. 1.3 hours for DDMA_{Ph}. Early digoxin may also be responsible for decreasing the maximum time to death compared to merged digoxin: 5.1 hours vs. 3.8 hours; however, this difference could also be due to small sample size.

Discussion and conclusions:

The purpose of this study was to see if the addition of phenobarbital to the existing D-DMA/DDMA protocols would improve the efficacy and reliability of the medications. In this preliminary study, the addition of phenobarbital was associated with a decrease of 20% in average time to death. Because the phenobarbital group (N=52) was much smaller than the non-phenobarbital control group (N=255), the decrease in average time to death was not statistically significant at the usual 95% confidence level ($P < 0.05$). Actual statistical significance was $P = 0.2$, an 80% confidence level. As more data is collected, the larger sample size will more accurately delineate the statistical significance.

The importance of a patient dying an average of 15 minutes more quickly is debatable — for the patient, family at the bedside, or clinician. One author (Dr. Shavelson), who has attended more than 200 aid-in-dying deaths, believes that some aid-in-dying deaths may be too rapid — potentially leaving some families stunned and not yet acclimated to the impending death. Time passed with an unconscious patient actually provides an adjustment period between conversing with an awake patient and looking death in the face; deaths less than 60 minutes after ingestion risk jeopardizing this potential adjustment. Thus, the additional speed of phenobarbital, is not necessarily a clinical blessing for the families of patients who die very quickly.

That being said, the addition of phenobarbital is definitely advantageous to “pull in the outliers,” those patients who take longer than average to die. The maximum time to death of 5.1 hours with phenobarbital-containing regimens is a significant improvement over the maximum of 12.4 hours observed in the comparison data with non-phenobarbital regimens. That difference makes the longest aid-in-dying deaths much easier for waiting families to patiently endure.

Adding phenobarbital to existing protocols seems to have paradoxically prolonged the average time to sleep, from 5.8 to 8.2 minutes. This conclusion, though, depends on the accuracy of the numerical data — which is not yet standardized. The definition of “time to sleep” is vague, with some using “time to coma” (equally ambiguous). At the bedside, there really is not a defined moment of “sleep,” and observers who report the times vary from doctors to nurses to volunteers to family members, all selecting a moment in time of a poorly delineated event. Alas, we take these time-to-sleep numbers with a grain of, well, sleep-sand in our eyes. Time to sleep of less than ten minutes is well within reasonable clinical expectations.

When comparing results between the D-DMAPh and DDMAPh groups, times to death were slightly faster in the early-digoxin group. The same trend has been seen in all prior studies when digoxin was given 30 minutes in advance of the other medications. This supports the hypothesis that digoxin absorption occurs more quickly or reliably using early-digoxin medication regimens than when the digoxin is merged with the other medicines in the regimen; 100 mg of digoxin may be better absorbed in the duodenum when ingested alone, rather than when competing with the 29,000 mg of other medications for absorption. However, it is not clear whether the quicker action of early digoxin is of benefit to families of patients who are prescribed the already-faster phenobarbital-containing drug regimens.

An important note: The authors have heard one anecdotal report of a 10-hour D-DMAPh death, but data from this death was not officially reported as part of this study. In addition, we have heard of deaths longer than the reported 12.4 hours with non-phenobarbital protocols. It is our firm belief that rare, individual patients with significant and sometimes unexplained “cardiac resilience”¹² will have significantly prolonged deaths, independent of the medication regimen used. This has been documented for every aid-in-dying protocol, especially with the earlier medication regimens that contained propranolol instead of amitriptyline, with the longest documented time to death of 39 hours. When using secobarbital alone, a death was reported to occur 4.3 days after ingestion. Fortunately, these idiosyncratically long aid-in-dying deaths are quite rare, and becoming more so as each medication protocol improves over the prior. Both authors believe that long deaths will never disappear completely as long as patients are required to *ingest* medications.

Theoretical advantages of adding phenobarbital to D-DMA/DDMA protocols:

Phenobarbital is a barbiturate that can be transported across the gastric mucosa^{13 14 15}, making it the only drug in the current aid-in-dying regimens that can be partially absorbed before reaching the small intestine.^{16 17 18 19 20} This might be helpful in patients with delayed gastric emptying (gastroparesis), which is present in many of our dying patients.

Upon reaching the brain, phenobarbital binds with the GABA receptors and affects them differently than benzodiazepines or opiates,²¹ Thus, the addition of phenobarbital to the morphine and diazepam of D-DMA/DDMA can augment the sedative and respiratory suppression effects of those protocols.

Phenobarbital has a well-known anticonvulsant effect, which could theoretically reduce or prevent the occurrence of terminal seizures in predisposed patients (those with brain metastases, strokes, or other brain lesions), especially because amitriptyline has been reported to lower the seizure threshold.

Finally, adding phenobarbital to the standard aid-in-dying protocols would create a single medication regimen for all patients, including those with additional risks. Before this study was undertaken, phenobarbital had been added on a case-by-case basis to aid-in-dying protocols for a subset of challenging patients: those with significant opiate/benzodiazepine tolerance, brain lesions, gastroparesis, or when a doctor was concerned that it might take the patient a significantly longer time to die. By uniformly adding phenobarbital to all life-ending regimens, less time may be required for prescribing physicians to closely follow their patients for the evolution of risk factors which can complicate and/or prolong an aid-in-dying death.²²

Conclusion: The authors recommend that aid-in-dying physicians add phenobarbital to D-DMA or DDMA, creating D-DMA^{Ph} or DDMA^{Ph}, as a standard protocol for medical aid in dying. D-DMA or DDMA are still acceptable options, especially if the patient is monitored for risk factors and phenobarbital is added when indicated. If further data confirms these preliminary results, the authors recommend a gradual conversion to phenobarbital-containing protocols for all aid-in-dying patients.

The American Clinicians Academy on Medical Aid in Dying requests that aid-in-dying physicians who use these now-recommended phenobarbital protocols contribute to continued data collection by completing the Academy's 2-minute [Death Data Reports](#). The Academy will continue to monitor the new protocol's use, and notify prescribing doctors and the aid-in-dying community at large of the results.

This article can be downloaded at: <https://www.acamaid.org/pharmacologyinfoupdates/>

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