

formulations and devices (such as autoinjectors, transdermal patches, and inhalers) known in the art which are compatible with Pro-2-PAM and/or the huperzine compound, such as +HupA.

[0107] Since Pro-2-PAM is relatively unstable in solution for an extended period, in some embodiments, Pro-2-PAM is maintained in its solid powder form just prior to use. In these embodiments, an autoinjector having a first compartment for storing the solid powder and a second compartment for storing the liquid solvent in which Pro-2-PAM is dissolved in just prior to injection may be used. See e.g. Clair et al. (2000) *Eur J Pharm Sci* 9:259-263. In embodiments where Pro-2-PAM is to be administered at the same time as the huperzine A compound, such as +HupA, the liquid solvent in which Pro-2-PAM is to be dissolved may comprise the huperzine A compound. Since Pro-2-PAM is readily dissolved in a slightly acidic solution, e.g. 0.9% sodium chloride, pH 5, and +HupA is also soluble in acidic solution, in some embodiments, the liquid solvent is an acidic solution.

[0108] In order to administer Pro-2-PAM prior to cholinesterase aging by an OP compound, the mixing time for dissolving Pro-2-PAM in solution is preferably less than about 30 sec. Thus, in some embodiments, the device used to deliver Pro-2-PAM comprises a mixer which rapidly mixes the Pro-2-PAM into solution just prior to delivery, i.e. as the injection mechanism is triggered.

[0109] In some embodiments, Pro-2-PAM and/or the huperzine A compound are, alone or in combination, microencapsulated or delivered in a liposome.

Additional Combination Therapies

[0110] The methods and compositions of the present invention may further comprise at least one supplementary active compound. Suitable supplementary active compounds, which are known in the art, include anticholinergics, anticonvulsants, carbamates, benzodiazepines, antiepileptics, barbiturates, anesthetics, oximes, and prodrug forms thereof. As used herein, a “prodrug” refers to a compound that, when administered to a subject, is converted *in vivo* into a compound that is active or significantly more active than the prodrug itself.

[0111] As used herein the term “anticholinergic” means any chemical, drug or drug effect that causes partial or total blockage of the action of the neurotransmitter acetylcholine. Examples include anisotropine, atropine, belladonna, clinidium, dicyclomine, glycopyrrolate, homatropine, hyoscyamine, mepenzolate, methantheline, methscopolamine, pirenzepine, propantheline, hyoscyne, aprophen, azapropen, benactyzine, biperiden, procyclidine, and the like.

[0112] Examples of anticonvulsants include acetazolamide, carbamazepine, clobazam, clonazepam, diazepam, divalproex sodium, ethosuximide, ethosin, felbamate, fosphenytoin, gabapentin, lamotrigine, levetiracetam, mephentermine, metharbital, methsuximide, methazolamide, oxcarbazepine, phenobarbital, phenytoin, phenisuximide, pregabalin, primidone, sodium valproate, stiripentol, tiagabine, topiramate, trimethadione, valproic acid, vigabatrin, zonisamide, avizafone, dihydrodiazepam, midazolam, and the like.

[0113] As used herein the term “carbamate” refers to derivatives of carbamic acid, including salts and esters, including urethanes (ethyl esters of carbamic acid). Examples include rivastigmine; neostigmine; pyridostigmine; physos-

tigmine; thiaphysostigmine; phenserine; norphysostigmine; physostigmine salicylate, Aricept®, donepezil, galanthamine, or the like.

[0114] As used herein, a “benzodiazepine” is a compound having a core chemical structure that comprises a benzene ring fused to a diazepine ring. Examples include chlordiazepoxide, diazepam, midazolam, imidazenil, avizafone, dihydrodiazepam, midazolam, and the like.

[0115] As used herein, a barbiturate is a compound that acts as a CNS depressant. Examples include allobarbitol, amobarbital, aprobarbital, alphenal, barbital, brallobarbitol, phenobarbital, and the like.

[0116] Suitable anesthetics include procaine, amethocaine, cocaine, lidocaine, prilocaine, bupivacaine, levobupivacaine, ropivacaine, mepivacaine, dibucaine, desflurane, enflurane, halothane, isoflurane, methoxyflurane, nitrous oxide, sevoflurane, and the like.

[0117] Suitable oximes include 2-PAM, Pro-2-PAM, obidoxime, methoxime, HI-6, HLo-7, TMB-4, monoisonitrosoacetone, diacetylmoxime, MMB-4, those set forth in U.S. Pat. No. 3,962,447, bis-oximes such as those set forth in Hammond et al. (2008) *J Pharmacol Exp Ther* 307(1):190-196, Pang Y—P et al. (2003) *Chem Biol* 10:491-502, and the like.

Dosages and Kits

[0118] Pro-2-PAM, a huperzine A compound, e.g. +HupA, or both may be provided in a kit as a single dose or as multiple doses, alone or in combination with one or more doses of at least one supplementary compound. In some embodiments, a single dose is a therapeutically effective amount. Determination of a therapeutically effective amount and timing of administration of a given compound is well within the capabilities of those skilled in the art, especially in light of the detailed disclosure herein. The amounts given below are a guideline and those skilled in the art may optionally titrate doses or use graded doses of an agent to achieve desired activity and minimize side effects in a treated subject.

[0119] A therapeutically effective amount of 2-PAM ranges from about 1 to about 30 mg/kg, preferably about 8 to about 26 mg/kg, more preferably about 8.6 to 25.7 mg/kg. Typically, dosages range from 0.2 mg/kg/day to 30 mg/kg/day.

[0120] A therapeutically effective amount of atropine is about 0.03 to 20 mg/kg, preferably about 0.03 to about 16 mg/kg. Typically, dosages range from 0.2 mg/kg/day to 20 mg/kg/day.

[0121] A therapeutically effective amount of Pro-2-PAM ranges from about 1 to 40 mg/kg, preferably about 8 to about 34 mg/kg, more preferably about 11 to 34 mg/kg, most preferably about 17 mg/kg. Typically, dosages range from 0.2 mg/kg/day to 40 mg/kg/day.

[0122] A therapeutically effective amount of a huperzine compound ranges from about 0.2 mg/kg to 100 mg/kg, preferably about 1 mg/kg to about 52 mg/kg. Typically, dosages range from 0.2 mg/kg/day to 100 mg/kg/day.

[0123] To the extent necessary to understand or complete the disclosure of the present invention, all publications, patents, and patent applications mentioned herein are expressly incorporated by reference therein to the same extent as though each were individually so incorporated.

[0124] Having thus described exemplary embodiments of the present invention, it should be noted by those skilled in the art that the within disclosures are exemplary only and that various other alternatives, adaptations, and modifications