Neurodegenerative Disorders: Science, Law, and Ethics

(The Ethics of Neuroscience)

Academy of Neurologic Communication Disorders and Sciences
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OUTLINE

I. Definitions of neuroethics (specifically, the “ethics of neuroscience”)

- “Neuroethics is the examination of what is right and wrong, good and bad about the treatment of, perfection of, and unwelcome invasion of or worrisome manipulation of the human brain.” (Safire, 2002)

- “Neuroethics is more than just bioethics for the brain . . . [it is] the examination of how we want to deal with the social issues of disease, normality, mortality, lifestyle, and the philosophy of living informed by our understanding of underlying brain mechanisms.” (Gazzaniga, 2005)

- “[Neuroethics is] a discipline that aligns the exploration and discovery of neurobiological knowledge with human value systems.” (Illes, 2006)

- The ethics of the practice of neuroscience addresses “the implications of our mechanistic understanding of brain function for society . . . integrating neuroscientific knowledge with ethical and social thought.” (Roskies, 2002, p. 21)

- “. . . the single most important integrative goal underlying neuroethics is a practical one: the need to improve patient care for specific patient populations. Hence, technological advances should always be discussed in light of their potential contribution to the good of the patients and the public.” (Racine, 2008, p. 3)


II. Major challenges associated with our care of patients with neurodegenerative disorders

a. Doing the best for our patients in the face of clinical uncertainty
b. Staying abreast of rapid research and technological advances
c. Using law to inform clinical and research practices
d. Identifying, discussing and resolving ethical issues
III. Patient-professional relationship (see Table: Cross-Walk Among Legal Duties, Moral Values, ASHA’s Code of Ethics and ANCDS’s Code of Ethics and Code of Conduct)

a. Fiduciary (trust, loyalty, beneficence)
b. Duty (beneficence, nonmaleficence)
c. Duty of care; standard of care (beneficence, nonmaleficence)
d. Negligence (nonmaleficence)
e. Excerpts from ANCDS Code of Ethics and Code of Conduct
   i. Preamble: “The Code of Ethics is designed to assure that all individuals holding membership and/or certification in ANCDS are committed to principled reasoning when making decisions, solving ethics quandaries, and making difficult choices in their professional lives and on behalf of individuals with neurologic communication disorders, and others, . . . “
   ii. Purposes: [T]he purposes of the ANCDS Code of Ethics and Code of Conduct are
       • “To embrace the notion that our work entails a moral dimension because we engage in clinical service, education, and research on behalf of individuals with neurologic communication disorders, and for the good of others;
       • “To recognize that our work entails making difficult choices in complex or uncertain situations that are best guided by a core set of moral and ethics principles;
       • “To embrace the notions that moral awareness, prudence in moral reasoning, and integrity of character are the foundations of beneficence, and must evolve with advances in scientific and clinical knowledge. . . .”

IV. Clinical ethics issues (adapted from Gauthier et al., 2013)

a. Standard of care; duty of care
b. Disclosure of diagnosis or probabilities about risk, e.g., disclosure of genetic or genetic susceptibility testing
   i. Individuals who are at risk but asymptomatic and cognitively normal
   ii. Individuals who have mild cognitive impairment
   iii. Individuals who have dementia with an uncertain future course
c. Efficacy of behavioral, pharmacological and genetic treatments
d. Informed consent; competency of patients with dementia to consent to reasonable and effective—or experimental—alternative treatments (or consent by a legally authorized representative);
e. Risk/benefit and cost/benefit of treatments
f. Uncertainty of diagnosis based on clinical presentation and biomarkers
g. Uncertainty of prognosis due to disease heterogeneity
h. Quality of life; social stigma of dementia; distress, depression
i. Impact on families and caregivers; support and counselling
j. End-of-life care; privacy and dignity

V. Research ethics issues (adapted from Emanuel et al., 2000)

a. Standard of care; duty of care (e.g., 45 CFR 46 & 21 CFR 56)
b. Social or scientific value
c. Scientific validity
d. Fair subject selection
e. Favorable risk-benefit ratio
f. Independent review
g. Informed consent; competency of patients with dementia to consent to research (or consent by a legally authorized representative); therapeutic misconception
h. Respect for potential and enrolled subjects
VI. Legal aspects

a. Federal law (Constitutional, statutory, regulatory, and case law)
   i. Liberty interest
   ii. Equal protection
   iii. Health (ACA)
   iv. Privacy (HIPAA)
   v. Nondiscrimination (e.g., GINA)
   vi. Human subjects protections
   vii. FDA regulations, e.g., expanded use
   viii. HHS regulations, e.g., conflict of interest

b. State (constitutional, statutory, regulatory, and case law)
   i. Self-determination, bodily integrity
   ii. Informed consent/refusal
   iii. Fiduciary obligations
   iv. Advance directives
   v. Malpractice; negligence
   vi. Licensure law (professional standards)

VII. Survey of legal and ethical issues surrounding the care of, and research with, individuals with neurodegenerative disorders

VIII. References and annotated bibliography

REFERENCES AND ANNOTATED BIBLIOGRAPHY

Select Publications

Addressing Law and Ethics for Clinical Aphasiologists


**Major Publications and Reports**


Secretary’s Advisory Committee on Human Research Protections (SACHRP), Subcommittee on Inclusion of Individuals with Impaired Decision-making in Research (SIHDR). (2008, March 27). Recommendations regarding research involving individuals with impaired decision-making. http://www.hhs.gov/ohrp/sachrp-committee/recommendations/2009-july-15-letter-attachment (See also 45 CFR 46.116. If a person lacks decisional capacity to consent to research, a “legally authorized representative” as defined by state law may consent.)


Select Parts of the Code of Federal Regulations


Food and Drugs. 21 CFR Part 50 (Protection of Human Subjects); Part 56 (Institutional Review Board). Retrieved November 1, 2016, from http://www.ecfr.gov/cgi-bin/text-idx?SID=be0d3d580f69df8dd0e8ecdf5d3558f64&mc=true&tpl=/ecfrbrowse/Title21/21cfrv1_02.tpl#0


Select Websites


Cutting Edge Science
Regarding Neurodegenerative Disorders


Summary of the science and ethics related to stem cell research.


An FDA approved drug (Buphenyl) was administered to Tau35 mice and "reversed the observed abnormalities in tau and autophagy, behavioural deficits, and loss of synapsin 1."


Describes imperfect relationship between clinical syndromes of PPA and frontotemporal lobe degeneration neuropathology (20-30% error); identifies a) FTLD-TDP (transactive response DNA-binding protein), FLTD-tau (the tauopathies), and AD (amyloid in Alzheimer’s disease). Calls for studies of clinicopathologic correlates using biomarkers (“a validated measure that reliably reflects the underlying pathology of a disease,” p. 5) associated with several different clinical syndromes: genetic, neuroimaging (MRI and PET of grey matter, white matter, or both), metabolic imaging (with PET using Pittsburgh Compound B [PiB]; and, biofluid analysis using CSF (cerebrospinal spinal fluid). Predicting underlying pathology is essential for development of “etiologically specific treatments” and “a potential cure” (p. 12).


Distinguishes primary tauopathies (“characterized by intracellular inclusions composed of abnormally-modified microtubule-binding protein, tau [MAPT], and Alzheimer’s disease (AD), including neurofibrillary tau and amyloid-beta plaques; and primary age-related tauopathy (PART), possibly an independent disease process of AD. Overlapping with cognitively normal (CN) aging, neurodegenerative syndromes may occur early or later in life, and are heterogeneous in presentation (AD, FTD variants, PSP, CBD, Picks; see Figure 2). “[A]ccurate ante mortem diagnosis of tauopathies is critical for the evaluation of these disease-modifying therapies targeting tau” (p. S30). See also Irwin et al., (2015). Frontotemporal lobar degeneration, Acta Neuropathologica, 129(4), 469-491.


Introduction of gene products to restore, replace, delete, or correct (edit) damaged cells shows promise. Challenges include gene delivery using viral or nonviral vectors, which vary in gene expression, duration, cellular specificity and safety (immune-mediated inflammation and oncogenesis are risks). Regarding neurodegenerative diseases, “transfer of the normal gene into diseased cells can correct the biochemical defect” or “neuroprophic factors may rescue diseased cells even when the gene defect is not known” or “RNA approaches may be used to suppress dominant-negative genes” (p. 281). The blood-brain barrier can be bypassed with intravenous or intraventricular injection (see Fig. 3, p. 283). Concludes: “Application of gene therapy . . . to the CNS will require breakthroughs in research on targeted gene delivery, controlled transgene expression, and methods to facilitate widespread correction of brain pathology” (p. 288).

CRISPR is a tool to edit genes; using the nuclease Cas9, the strands of DNA are “cut” precisely, leading to gene disruptions and inactivation of the gene, either in embryonic (dividing) cells or in somatic (nondividing) cells, and to “eliminate the expression of mutant genes” (p. 2), in the neurodegenerative diseases (e.g., huntingtin in HD; α-synuclein in PD), or to replace mutant genes with normal ones. Goals include generating animal models of neurodegenerative diseases (e.g., PD, HD; p. 2) and correcting or inactivating mutant genes as a therapeutic intervention. Challenges include off-target effects and “mosaic mutations” (p. 3). “Further evolution of the CRISPR/Cas9 system to increase targeting specificity and efficiency is expected to improve the knock-in rate and application of this genetic engineering tool to treat neurodegenerative diseases in the future” (p. 3). See also (a) Editorial (2016, March 10). Gene intelligence: The risks and rewards of genome editing resonate beyond the clinic. *Nature*, 53, 140 (b); Cyranoski, D. (2015, March 19). Embryo editing divides scientists. *Nature*, 519, 272 (discussing whether it is ethical to apply gene editing technology to reproductive [“germ line”], or should it be applied only to non-reproductive [somatic] cells).

**Ethics and Law**  
**Surrounding Clinical Care and Research of Individuals With Neurodegenerative Disorders**

*Alphabetical list of topics*

- Brain stimulation: DBS, tDCS, TMS  
- Compassionate use  
- Compensation for injury  
- Embryonic stem cell research  
- End-of-life decision-making; Refusal of life-sustaining treatment; Physician-assisted suicide  
- Incidental findings  
- Negligence; standard/duty of care; fiduciary duty  
- Personalized medicine; precision medicine  
- Placebo arms in clinical trials; “sham” arms in surgical trials  
- Predictive testing; Susceptibility testing  
- Preimplantation genetic diagnosis (PGD)  
- Prevention trials  
- Privilege: patient-doctor; participant-investigator  
- Special topics: Amyotrophic lateral sclerosis; Prion disease  
- Vulnerability  
- Waiver of liability

**Brain stimulation; DBS, tDCS, TMS**

**IS BRAIN STIMULATION FOR NEURODEGENERATIVE DISEASE BENEFICIAL (OR HARMFUL) TO PATIENTS?**


“There is insufficient evidence to determine the effects of tDCS for reducing off time (when the symptoms are not controlled by the medication) and on time with dyskinesia (time that symptoms are controlled but the person still experiences involuntary muscle movements), and for improving health-related quality of life, disability, and impairment in patients with IPD. Evidence of very low
quality indicates no difference in dropouts and adverse events between tDCS and control groups” (Authors’ conclusions, p. 2).


Discusses potential applications of TMS and tDCS to Alzheimer’s disease (AD), vascular dementia (VaD), dementia with Lewy bodies (DLB), Parkinson’s disease with dementia (PDD), frontotemporal dementia (FTD), and mild cognitive impairment (MCI). Studies involving patients with dementia, to date, includes 13 with AD, 4 with MCI, 1 with DLB, 14 with PD with no dementia, and none with VaD, PDD, or FTD. Regarding PD (without dementia), 12 of 14 studies reported benefits to motor function (noting methodological heterogeneity; possible placebo effect). Considerations include: frequency of stimulation, task specificity of benefit, short-term versus sustained benefit on cognitive measures, dementia severity, location of stimulation, and study design (stimulation alone or with cognitive training). Challenges for TMS and tDCS in dementia research include: concurrent use of psychotropic medications; presence of brain lesions and atrophy; distribution of CSF; definition of the specific symptom targeted; determining the best location for the stimulation; and determining optimal TMS and tDCS stimulation parameters (e.g., current density, stimulation frequency, number, frequency and duration of treatment sessions, and, intervals between sessions).


“There is currently insufficient evidence to draw conclusions about the efficacy and safety of rTMS in the treatment of ALS. Further studies may be helpful if their potential benefit is weighed against the impact of participation in a randomized controlled trial on people with ALS” (Authors’ conclusions, p. 2).


Risks associated with DBS are related to the device itself (e.g., electrode migrations or misplacements, infections, device malfunction; less frequently, hemorrhage, pneumonia, embolism), dose-dependent reversible side effects (e.g., gait alterations, though generally low affective or cognitive side effects). Effects vary based on patient group (e.g., dystonia, Parkinson’s) and other characteristics (younger patients with shorter disease duration generally do better than older patients with longer disease durations). “Albeit relatively small, the risk of associated adverse effects means that invasive therapies will usually be delayed until other treatment options have been exhausted and the suffering and limitations of quality of life perceived by the patient justify more invasive measures” (p. 77). Though clinical symptoms improve (e.g., motor benefits in PD), disease progression continues. Some evidence suggests that patients longer than 4 years duration with idiopathic PD benefit more than those with atypical PD. Authors address whether the criterion of therapy resistance is a valid reason to defer DBS. Concerns about DBS include a) surgical intervention, b) integration of a device in the body, c) reported feels of strangeness and danger, and d) direct intervention in the brain. Despite these perceived barriers, the authors make a case, organized around eight ethical principles, that “[r]estricting DBS to late courses of PD excludes the possibility of testing DBS in comparison to the best available successful standard therapy before major side effects or therapy resistance occurs” (p. 82).
IF ADVANCED PATIENTS WITH PARKINSON’S BENEFIT FROM DEEP BRAIN STIMULATION, WOULD IT BE ETHICAL TO USE DBS EARLY IN THE COURSE OF THE DISEASE (BEFORE LEVODOPA BECOMES INEFFECTIVE)?


DBS is an invasive procedure that has proven to be effective in ameliorating motor symptoms in advanced stages of the disease. It is ethically justified because no other treatment is available. A few studies showed that DBS improved quality of life and motor symptoms in early-stage PD but mood, affect, memory, behavior, language and swallowing were adversely affected. More clinical research, meeting the ethical requirements articulated by Emanuel, Wendler, and Grady (2000) are needed.

IS IT ETHICAL TO IMPLANT NOVEL DEVICES INTO THE BRAIN WITHOUT KNOWING THE LONGTERM PSYCHOLOGICAL AND SOCIAL EFFECTS, PARTICULARLY IMPACTING VULNERABLE INDIVIDUALS WHO HAVE NO OTHER TREATMENT OPTIONS?


Ethical concerns include: identity, normality, authority, responsibility, privacy and justice. Devices include deep brain stimulators (Parkinson’s disease), transcranial direct current stimulation (tDCS), and implantation of brain sensors coupled to robots for individuals who are paralyzed.

"Compassionate use" of experimental drugs

WHEN INVESTIGATORS PROMISE TO PROVIDE AN EXPERIMENTAL TREATMENT TO PATIENTS IN A CONTROL GROUP (PLACEBO OR SHAM), IS IT ETHICAL TO WITHHOLD THE TREATMENT AFTER THE TRIAL?


Plaintiffs with Parkinson’s disease participated in a double-blind placebo controlled trial of glial cell line-derived neurotropic factor (GDNF) designed to stop the death of dopamine cells. The study had a large placebo effect and that did not demonstrate efficacy. Participants then enrolled in an open-label study. The informed consent document stated they could “elect to continue treatment for up to an additional 24 months” after the study had ended, but Amgen refused to provide GDNF off-protocol due to safety and efficacy concerns. The FDA approved GDNF for compassionate use, but again Amgen refused. The court denied plaintiff’s request for an injunction. Amgen (sponsor) had no fiduciary duty and no contract with plaintiff (i.e., Amgen’s contract with the University of Kentucky was not a binding contract on Amgen) and Amgen “had sufficient scientific reasons to terminate the study based on the safety concerns” (p. 23).

*Dahl v. HEM Pharmaceuticals*, 7 F.3d 1399 (Ct. App. 9th Cir., 1993).

Patients with chronic fatigue syndrome participated in a double-blind randomized placebo-controlled study in which the consent form promised the experimental drug for 12 months upon completion of the study. The court ordered HEM to provide it. On appeal, the court upheld the injunction and ordered HEM again to provide the drug for patients who wanted it (even though the
FDA did not issue a treatment IND) and if they agreed to participate in the FDA-approved open label study that was currently underway.

**IS COMPASSIONATE USE OF INVESTIGATIONAL DRUGS ETHICALLY APPROPRIATE?**


Post-Trial Provisions (Para 34):

In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.


Despite arguments against compassionate use, authors acknowledge society’s motivation—duty to rescue: “When people face dire outcomes, we are compelled, morally and psychologically, to try to help them. We do not feel a need to justify this for any reasons other than compassion for their plight” (p. 16).


Three states (CO, MO, LA) have passed “right to try” laws to give patients access to drugs unapproved by the FDA. Nevertheless, author explains that it is reasonable for companies to say “no” because a) it is a distraction from the aim to establish a drug or treatment safe and effective; b) it redirects resources; c) it undermines randomized trials; d) adverse off-protocol events can derail promising treatments; e) the practice may not be a just allocation of resources.


Expanded Access Program (FDA, 2009) considers use of investigational drugs and biologics to be a “clinical investigation,” subject to ethics review and data reporting requirements.


Regarding special access programs: “SAPs are problematic, given their capacity to threaten regulatory protections and the development of medical knowledge. . . . SAPs should play a mandated role in knowledge generation . . . [thereby imposing] an obligation on patients participating in SPAs to agree to data collection” (p. 4). Article summarizes requirements SAPs in United States, Canada, Australia, and Europe.

**Compensation for injury**

**SHOULD RESEARCH PARTICIPANTS BE COMPENSATED FOR ANY INJURIES RESULTING FROM PARTICIPATION IN BIOMEDICAL RESEARCH?**

General Principles (Para. 15):
Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

See also: Moral Science (2011), Appendix III (DoD, DVA, Medicare, NASA, NIH Clinical Center, U Cal Los Angeles, U Washington, and Wake Forest University provide for research related injury costs); Appendix IV (a survey of over 40 countries’ provision for compensation for research injuries).

Embryonic stem cells

IS IT ETHICAL TO USE EMBRYONIC STEM CELLS (EBSS) OR INDUCED PLURIPOTENT STEM CELLS (IPSCS) TO TREAT NEURODEGENERATIVE DISORDERS WHEN NO OTHER EFFECTIVE TREATMENT IS AVAILABLE?


Using stem cells for the purpose of replacing and restoring cells lost through neurodegeneration has been examined in PD, MS, HD, MSA, Motor neuron disease and others (see Table 1). “A stem cell is defined as a cell that has the ability to continuously divide and differentiate (develop) into various other kind(s) of cells/tissues” (p. 64). Theoretically, they can be grafted to replace lost cells; they can be harvested from the patient and then used therapeutically, and they can be developed into a relevant cell type then tested in vitro to identify therapeutic agents (p 64). Sources are: embryonic, fetal, and adult (i.e., adult somatic cells harvested then reprogrammed to pluripotency). The article describes the early trials designed to replace dopamine cells in PD; many patients benefited, but were not protected from disease progression. Ethical issues include the source of cells (embryos and fetal tissue), the compromised decision-making capacity of affected patients, patient selection criteria (i.e., more advanced disease in whom standard therapy has failed), and the problem of “stem cell tourism” for as yet unproven therapies, and the need for double blind placebo controlled trials with adequate power.


Some benefit for younger patients. Several developed dystonia and rigidity. (See Piantadosi, S., 2010 for a review.)


The common thread among the various neurodegenerative disorders is atypical protein formation and induction of cell death. The source of cells can be embryonic or somatic; the latter can be reprogrammed to produce pluripotent stem cells by nuclear transfer into oocytes or by fusion with ESCs, but newer work uses non-embryonic somatic cells, then reprograms them, producing induced pluripotent stem cells (iPSCs). To date, no patient iPSCs have been transplanted into humans (p. 11). Article details the scientific challenges and issues of patient selection (age, disease type, and duration), duration of any beneficial effect, and risks (e.g., tumorigenesis). (Compare Freed et al. 2001 regarding fetal stem cell transplantation.)
End-of-life decision-making; Refusal of life-sustaining treatment; Physician-assisted suicide

Fourteenth Amendment to the U.S. Constitution, Section 1 (ratified July 9, 1868).

Liberty interest and equal protection:

Section 1. All persons born or naturalized in the United States and subject to the jurisdiction thereof, are citizens of the United States and of the State wherein they reside. No State shall make or enforce any law which shall abridge the privileges or immunities of citizens of the United States; nor shall any State deprive any person of life, liberty, or property, without due process of law; nor deny to any person within its jurisdiction the equal protection of the laws.

IN THE UNITED STATES, MAY STATES SET THE LEGAL STANDARDS ASSOCIATED WITH WITHDRAWAL OF LIFE-SUSTAINING MEDICAL TREATMENT?

In *Cruzan v. Dir., Missouri Dept. Health*, 497 U.S. 261 (June 25, 1990). Holding: that the State of Missouri did not offend the 14th Amendment to the U.S. Constitution by requiring a “clear and convincing” level of evidence before allowing an incompetent individual to withdraw life-sustaining medical treatment. In this case, the patient was Nancy Beth Cruzan, who had sustained a grave head injury in an automobile accident 7 years earlier and was not competent to decide for herself. Her father desired to decide as she would have decided for herself but failed to provide “clear and convincing evidence” of her wishes to the Missouri court. After the U.S. Supreme Court decision, additional evidence was presented to the Missouri court and Nancy Beth’s feeding tube was withdrawn.

IN THE UNITED STATES, DO INDIVIDUALS HAVE A RIGHT TO PHYSICIAN-ASSISTED SUICIDE?

The U.S. Supreme Court found no right to physician-assisted suicide (PAS).

*Washington v. Glucksberg*, 521 U.S. 702 (June 26, 1997). Washington State’s legislative prohibition of PAS is legitimate because PAS is not a fundamental liberty interest protected by the due process clause of the Fourteenth Amendment; the statutory prohibition does not place an undue burden on competent terminally ill adults’ constitutionally protected liberty interest because it is reasonably related to a legitimate state interest in protecting human life.

*Vacco v. Quill*, 521 U.S. 793 (June 26, 1997). Refusing life sustaining treatment and requesting physician assisted suicide are legally distinct. The right to refuse life-sustaining treatment is based on “traditional rights to bodily integrity and freedom from unwanted touching” (*Cruzan*, 1990, 497 U.S. at 278-279). Holding that New York State’s law prohibition on assisting suicide does not violate the Equal Protection Clause of the Fourteenth Amendment.

States are free to establish the right to request physician assisted suicide, as several states have done (CA, OR, VT, WA by legislation; MT by court ruling; referendum in Colorado pending).

The Montana Supreme Court found that consent by a patient may be a viable defense for a physician who offers aid-in-dying.

*Baxter v. Montana*, 224 P.3d 1211 (2009). According to the Montana Supreme Court, analyzing statutes pertaining to the Rights of the Terminally Ill, suicide, and homicide, held that there is no public policy against allowing physicians to use a competent, terminally ill patient’s consent as a defense to a charge of homicide if the physician aids dying (by providing the lethal means) but where the patient does the act. Justice Nelson (concurring) argues a physician’s aid in dying is
protected by the privacy provision in the Montana Constitution and as a matter of individual dignity.

**Incidental findings: Duty to warn/duty to report?**

**SHOULD CLINICAL RESEARCH INVESTIGATORS HAVE A LEGAL DUTY TO REPORT TO PARTICIPANTS WHEN THEY DISCOVER “INCIDENTAL FINDINGS” OF POTENTIAL SIGNIFICANCE TO THE PARTICIPANTS?**


Four models: traditional consent, staged consent, mandatory return, and outsourcing (see Table 1, p. 24).


If one accepts that incidental findings are foreseeable, that the investigator-research participant is a fiduciary one, and that “those responsible for the design, approval, and implementation of the experiment . . . have a duty to protect human subjects both under the Common Rule [45 CFR 46] and common law” (p. 358) then liability should attach to investigators who do not integrate the highest of standards in clinical research protocols (e.g., including a board-certified radiologist when reviewing research MRI scans), and include language in the informed consent form “disclos[ing] the potential that incidental findings of abnormalities might be revealed and what consequences might follow if they are” (p. 357). “The duty to a vulnerable research subject is independent of consent” (Grimes v. Kennedy Krieger Institute, p. 101). Including information about incidental findings in a consent form is important “because it may be material to the decision of whether or not to participate in the research” (p. 359).

**Note.** The IRB-approved consent form must include “A statement that significant new findings developed during the course of the research which may relate to the subject’s willingness to continue participation will be provided to the subject.” 45 CFR 46.116(b)(5) and 21 CFR 50.25(b)(5).


“Making progress in the debate over return of research results and incidental findings requires recognizing that the debate is fundamentally about the translational process. Return of information generated in the process of conducting research, because of the potential clinical importance of that information, is a practice that occupies the space between research and clinical care. . . .” (p. 447). This translational practice calls for the development of ethical and legal standards regarding who is responsible for returning information and to whom; the quality of the information returned; whether returning results or incidental findings should be part of the informed consent process; and, whether liability should attach to a failure to return results, particularly if the information might have prevented serious harm or death.”
Negligence (Medical malpractice; “Research malpractice”); Fiduciary duty of researchers

IS RESEARCH MALPRACTICE FOR HARMS RESULTING FROM NEGLIGENCE DURING A MEDICAL STUDY A WIDELY RECOGNIZED CAUSE OF ACTION?

Some jurisdictions use the standard of medical malpractice (e.g., Halushka v. University of Saskatchewan, 1965; Heinrich v. Sweet, 2002). Other jurisdictions recognized that medical researchers have a higher duty of care than a clinician based on the “special relationship” between investigator and participant (Grimes v. Kennedy Krieger, 2001), e.g., a “heightened duty for disclosure of foreseeable risks” (Whitlock v. Duke, 1986, discussed by Jansson, 2003, p. 240) and in Moore v. Regents, wherein a physician has a fiduciary duty to his patients, namely, a duty to disclose financial conflicts of interest. Sources for determining the standard of care are the federal regulations and expert testimony, state statutes governing medical research (e.g., New York, California), and case law.


General Principles (Para 9)
It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent. (p. 2191)


Describing a “special relationship” between investigator and participant from which legal duties arise; lead abatement studies involving children violated involved nondisclosure of risks, coercion of parents, and violation of the “minimal risk” rule in a nontherapeutic context. See also www.sskrp.com


An early Canadian case distinguishing between medical practice and medical research; patient suffered cardiac arrest and brain damage after undergoing research involving heart catheterization using a new and untested anaesthetic agent. “The subject of medical experimentation is entitled to a full and frank disclosure of all the facts, probabilities and opinions which a reasonable man might be expected to consider before giving his consent. The respondent necessarily had to rely upon the special skill, knowledge and experience of the [researchers], who were . . . placed in the fiduciary position. . . .” [para 28]).

Heinrich v. Sweet, 308 F.3d 48 (Ct. App. 1st Cir. 2002).

Case involving death of plaintiff with GBM undergoing combined radiation and chemotherapy; using the medical negligence model in the clinical research context.

Moore v. Regents of Univ. of Cal., 793 P.2d 479 (Cal. 1990).

Involving derivation of a patented cell line from patient’s spleen cells without his knowledge; court held he had no property interested in harvested tissue but that the investigators owed him a fiduciary duty and should have disclosed their conflict of interest during the consent process.
An experienced “diver” alleged cerebral damage during an experimental simulated deep-dive, saying that Duke researchers did not inform him of the risks of air emboli during decompression. The court held that Duke met the informed consent requirement as defined by the federal regulations (Common Rule). Makes reference to both the Nuremberg Code and the Declaration of Helsinki, and asserts, “the degree of required disclosure of risks is higher in the nontherapeutic context” (p. 1471).


Builds a case for research malpractice (as distinct from medical malpractice); advocates for using expert testimony to determine negligence for inadequate informed consent; suggests that IRB approval should serve as a partial defense.

ARE CLINICIANS LIABLE FOR FAILING TO REFER FOR, OR MAKING ERRORS IN THE APPLICATION OF TECHNOLOGY FOR PREIMPLANTATION GENETIC DIAGNOSES (PGD) FOR INHERITED NEUROLOGICAL DISORDERS VULNERABLE TO LAWSUITS?


Lawsuits arise for lack of informed consent, negligence in performing or failure to perform, failure to disclose inexperience and nondisclosure of inherent errors associated with PGD leading in some cases to the birth of a child with a defect. Reviews published case law. Causes of action include: wrongful birth, wrongful life, and failure to inform.

Personalized medicine; precision medicine

DO MEDICAL PROFESSIONALS AND LAYPERSONS UNDERSTAND “PERSONALIZED” (“PRECISION”) MEDICINE?


In the wake of the Human Genome Project focus “personalized [genomic] medicine” is now referred to as “precision medicine.” Authors report that the rebranding signifies a shift “away from ‘patient empowerment’ and toward expert-mediated decision-making” (p. 22), and “broaden[s] the movement’s focus from ‘individualizing treatments for particular patients to using genomic profiling on behalf of the interests of extended families, minority groups, and national populations” (p. 22). Citing the U.S. President’s Council of Advisors on Science and Technology (Priorities for Personalized Medicine, 2008, September): “personalized medicine . . . does not literally mean the creation of drugs or medical devices that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or response to a specific treatment” (https://www.whitehouse.gov/files/documents/ostp/PCAST/pcast_report_v2.pdf) – namely categorizing patients by genetic risk and therapeutic efficacy “based on what is known about the subsets of the population with their genotypes” (p. 23). Ethical implications include a shift of the clinician’s role to that of informational gatekeeper and censor and, more dire, to “involuntary genetic testing and disclosure” (p. 27).
WHAT ARE THE EDUCATIONAL STANDARDS AND INTERPRETIVE SKILLS NEEDED BY PHYSICIANS WHEN THEY MAKE CLINICAL DECISIONS BASED ON GENETIC INFORMATION?


Describing a case where a 13-year old boy died suddenly, presumably of QT syndrome although genetic testing at autopsy (so-called “molecular autopsy”) was not done. Subsequent commercial genetic testing done on the surviving family members (so-called “surrogate” genetic testing) was deemed to confirm a familial mutation, placing them all at risk for sudden death. One of the deceased boy’s brothers had a defibrillator implanted. Subsequent genetic analysis at Mayo revealed that the original diagnosis was erroneous. “[T]he mere presence of a rare variant in a bona fide LQTS-susceptibility gene . . . does not guarantee that variant’s pathogenicity” (p. 1614). “The interpretation of findings has always been and will always be a cornerstone of genetic interrogation and precision medicine”; . . . phenotyping still matters most” (p. 1615, emphasis added).


**Placebo arms in clinical trials; “sham” arms in surgical trials**

ARE “SHAM” ARMS IN AN "RCT" PROTOCOL ETHICALLY APPROPRIATE?


Use of Placebo (para. 33):

The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.


Defends sham surgery controls, arguing that participants’ social obligations are sufficient to outweigh burden to individuals randomized to sham arms of a controlled trial (when certain criteria to assure rigorous research design are in place).

A widely cited article discussing (and defending) the use of sham surgery as a placebo control.


A widely cited article discussing the reasons why sham surgery is not ethically acceptable.


Reviews gene-based and cell-based neurosurgical interventions for PD, including adrenal medullary transplantation (no sustained benefit; significant adverse events), fetal dopaminergic cells transplantation (no clinical benefit between true and sham neurosurgical arms), and other agents, e.g., glial cell-line-derived neurotrophic factor (GDNF), neurturin, retinal pigment epithelial cells (limited or no benefit in controlled trials). Discusses trial design, the placebo effect, risks of the sham arm (including partial burr hole), integrity of informed consent in individuals with cognitive impairments, significant use of resources to conduct the trials, and “circumstances under which the investigational agent will be available” after the trial.


Critical review of trials involving transplantation of fetal mesencephalic cells, fetal nigral cells, fetal dopamine cells, fetal embryonic mesencephalic cells, embryonic dopamine neurons, and glial cell-line derived neurotrophic factors (GDNF). “Trials are plagued by presupposition of benefit, lack of masking, and multiplicity. I suspect all these limitations and others were clearly evident in the study protocols. All the positive results appear to be placebo effects, bias, or type 1 errors.” (Piantadosi, 2010, slide 22). Summarizing Freed, C. R., Greene, P. E., Breeze, R. E., et al. (2001, March 8). Transplantation of embryonic dopamine neurons for severe Parkinson's disease. *New England Journal of Medicine, 344*(10), 710-719:

- N=40 random treatment assignment with the supposition that therapy was effective (subjects were assured that they could receive transplantation later, helping to justify the sham surgery)
- Masked
- Post hoc recipient age stratification was presented as the primary outcome
- No overall effect
- How would transplanted cells know how old the new brain is? (Piantadosi, 2010, slide 9)

“The first of these studies were published 18 years ago. They had substantial methodological shortcomings unnecessary for the day and not acceptable today. 18 years later we are still using the same study “designs” and analyses that have the potential to mislead.” (slide 23)

**See also:**

Predictive genetic testing; Susceptibility testing

DOES PREDICTIVE TESTING FOR EARLIER IDENTIFICATION OF NEURODEGENERATIVE DISEASES DO MORE HARM THAN GOOD?


“Up to now, the identification of genes responsible for adult neurodegenerative disorders has helped elucidate molecular mechanisms underlying the etiology and pathogenesis of these disorders. Such discoveries have begun to impact biomarker development and drug discovery, but have not yet led to improved treatments or prevention” (p. 3). Comprehensive review of the genetics of HD, AD, PD, FTD, ALS, and prion disease. Focus on studies examining health-related quality of life (HRQOL, both generic and disease-specific); emphasis on using HRQOL measures in *clinical trials* and *predictive testing research*, including not only motor aspects of disease but also language, memory, balance, interpersonal relationships, employment concerns, and coping. Identifies genetic discrimination (defined as “the denial of rights, privileges, or opportunities or other adverse treatment based solely on genetic information” (p. 10)) as a barrier to “uptake” of predictive testing (e.g., for HD, update is 10-20%). Predictive testing aims to reduce morbidity and mortality through screening, observation, early treatment or prevention. “What makes a genetic test ‘predictive’ is typically a highly penetrant gene that determines a specific disease as an outcome” (p. 12), as distinct from susceptibility or risk assessment such as ApoE4 variants in AD. Arguments against predictive testing are their probabilistic nature, the fact that “the absence of a specific genetic risk factor does not ensure that an individual has no risk of developing [the disease]” (p. 14), and that “the availability and value of an intervention” (p. 14) are highly variable across the types and stages of neurodegenerative diseases. However, the authors note that “many participants experienced significant benefit from predictive testing, even in the absence of treatment” (p. 14). HRQOL studies reviewed in this article report benefits such as knowledge and understanding, life planning, connections with others, life meaning and insight, social support, and hope and optimism (see Figure 2, p. 12).

IS IT LEGAL FOR INSURANCE COMPANIES TO DISCRIMINATE AGAINST INDIVIDUALS BASED ON “PREDICTIVE NEUROSCIENCE” INFORMATION (E.G., BIOMARKER INFORMATION GLEANED THROUGH BRAIN SCANS, CSF ANALYSIS, ETC.)


Individuals cannot be disadvantaged by health insurers based on predictive genetic information. Health Insurance and Portability Accountability Act (HIPAA, 1996), Genetic Information Nondiscrimination Act (at least until the disease manifests; GINA, 2008), and the Affordable Care Act (protecting preexisting conditions, a manifest medical problem; ACA, 2010). Predictive neuroscientific data do not enjoy the same protections under the law.
WHAT ARE THE ETHICAL ISSUES SURROUNDING SUSCEPTIBILITY TESTING IN INDIVIDUALS WITH NEURODEGENERATIVE DISORDERS?


Focus not on highly penetrant mutations in Huntington’s and autosomal dominant AD but rather on “lower penetrance alleles.” Authors address six questions. (1) When to test? A test should be used if it is reliable and has strong predictive value (APOE testing “has limited predictive value and there are currently no proven prevention options for AD,” p. 91). A genetics counselor should always be involved, which is often not the case with direct-to-consumer marketing of genetic tests. (2) Capacity and consent. Consent to susceptibility testing (and research in general) may be compromised by diminished capacity; if cognitive testing is undertaken to determine competency, practitioners may be careful of possible legal implications. (3) Risk estimation. Note that estimating risks from genetic tests alone is ill-advised, behavioral, environmental, comorbid conditions, social determinants are factors that must be considered. (4) Communicating results. Traditionally, clinical geneticists and genetic counselors have been called upon to provide counseling, but “the emergence of genetic susceptibility testing for neurodegenerative diseases may force neurologists and allied health care professionals to assume a greater role in patient education” (p. 93). (5) Psychological and behavioral impact of results. In context of AD being an incurable and severe disease, post-testing support is essential. (6) Testing children. The consensus view is that, absent a medical benefit, asymptomatic minors should not be tested for susceptibility genes or carrier status. (See also Peters et al., 2013, discussing AD prevention trials.)

Preimplantation Genetic Diagnosis (PGD)

IS IT ETHICALLY ACCEPTABLE TO USE PREIMPLANTATION GENETIC DIAGNOSIS (PGD) OR PRENATAL TESTING IN AT‐RISK ADULTS FOR NEURODEGENERATIVE DISEASE THAT APPEAR LATER IN LIFE?


TGD is justifiable “when the conditions are serious and when there are no known interventions for the conditions or the available interventions are either inadequately effective or significantly burdensome” (p. 54). PGD involves embryo biopsy; long-term effects on the developing fetus are unknown. An experienced genetic counselor should be involved before PGD is undertaken.


“PGD for an autosomal dominant late-onset disease with full penetrance of the mutation and the example of HD Some critics argue that testing for late-onset disease is unjustified, because the child will probably have several decades of unimpaired living and the disease may become treatable. This critique, however, is debatable in case of HD, for example, since it is a serious, even lethal, disorder and has complete penetrance of the underlying mutation. A person found to have a mutation would inevitably get the symptoms in the future. Symptoms may appear from the late 20s, but more usually in the fourth or fifth decade. Furthermore, the prospect of the fate of the children who carry HD often imposes an extremely severe burden. HD is currently untreatable. A predictive test allows asymptomatic at-risk adults to know whether they have the Huntington mutation. The use of PGD for asymptomatic individuals with the Huntington mutation and
excluding embryos with the mutation is generally regarded as acceptable. New molecular tools have been developed improving the diagnosis for HD using PGD” (p. 596). 


Addressing predictive testing for adult-onset neurodegenerative conditions due to genetic mutations, and management of individuals within a family who differ in their desires for information.


Advocates integration of PGD into “modern preventative neurology,” because “most couples at risk of transmitting a genetic mutation would opt for PGD over prenatal testing and possible termination of a pregnancy.”

**Prevention trials**

**DO THE BENEFITS OF PREVENTION TRIALS OUTWEIGH THE RISKS?**


Despite several decades of research, “an effective disease-modifying treatment remains elusive” (p. 114). Like other neurodegenerative diseases, it is thought that the neural changes begin many years before disease onset, so early identification of asymptomatic and presymptomatic individuals is essential to research progress. Advocates (a) genetic risk stratification and (b) biomarker status (positive, negative; e.g., CSF levels of amyloid beta and tau, PET imaging, MRI measures of atrophy). Summarizes multi-center prevention trials under development to assure a large n and harmonized trial design.

The three main ethical concerns are a) scientific validity, b) benefits and risks, and c) diagnostic disclosure and disclosure of incidental findings. As for validity (see Fig. 2), authors note”

“Absent a surrogate biomarker to gauge treatment efficacy, the identification of appropriate primary outcome measures in asymptomatic individuals poses an immediate challenge. Clinical measures that are sensitive and specific to change over time in individuals without overt symptoms at trial onset, and who may not develop symptoms for many years remain the gold standard. . .

“Biomarkers may be helpful, but to date are unproven for longitudinal evaluation” (p. 117) . . .

“The potential circularity of using biomarkers both to determine subject eligibility for a trial and as an outcome measure to gauge efficacy for that trial is yet another challenge.” (p. 119)

As for benefits and risks, continual assessment and informed consent over the 5-year trial will be necessary as well as careful attention to data and safety monitoring. Confidentiality of genetic data, use of current genetic counseling guidelines (Goldman, Han, Catania et al., 2011, Genetics in Medicine, 2011), and a protocol for incidental findings are additional considerations.
IS IT ETHICAL TO DISCLOSE GENETIC AND BIOMARKER TEST RESULTS TO PARTICIPANTS IN PREVENTION TRIALS?


Prevention studies strive to recruit asymptomatic persons identified by various risk factors (genetic such as APOE-e4, or biomarkers such as amyloid). Ethical concerns that may arise include: (a) interventions may carry significant risks without offsetting benefits; (b) because many participants will never acquire the disease, they may incur harms from learning their biomarker status (e.g., anxiety, depression, stigma) without offsetting benefits; and, (c) if participants who are risk-positive later acquire the disease, no treatment is currently available. This paper explores the ethical dimensions of “transparent” versus “blinded” enrollment in the context of individuals’ “right not to know.”

“Privilege”: patient-doctor; participant-investigator?

DOES THE LAW RECOGNIZE A LEGAL RIGHT TO SHIELD RESEARCH DATA FROM DISCLOSURE?

*Cusumano v. Microsoft*, 162 F. 708 (1st Cir. 1998).

Disallowed a corporation’s motion to compel academic researcher’s research records (where the researchers had signed nondisclosure agreements and had entered into confidentiality agreements with interviewees), because, on balance, “compelling the disclosure of such research materials would infrigidate the free flow of information to the public, thus denigrating a fundamental First Amendment value” (p. 717).


Most courts do not recognize a researcher-participant privilege. “Professional academic freedom, although it is endorsed by numerous educational associations, has no direct legal effect and is not embraced within the current case law” (p. 380, citing Briggs, W. K., (2013). Open-records requests for professors’ email exchanges: A threat to constitutional academic freedom? *Journal of College and University Law, 39,* pp. 603-604). See also *Cusumano v. Microsoft Corp.*, 162 F.3d 708 (1st Cir. 1998) (concluding “[a]cademicians engaged in pre-publication research should be accorded protection commensurate to that which the law provides for journalists,” p. 714).


Reviews published cases involving challenges to HHS certificates of confidentiality (designed to protect against compelled disclosure in response to a subpoena) which are consistent with IRB rules (45 CFR 46). Discusses the procedural requirements and the vulnerabilities; also discusses layered state laws and regulations pertaining to research data.
Special ethics topics

WHAT ARE THE SPECIAL ETHICS CONSIDERATIONS IN AMYOTROPHIC LATERAL SCLEROSIS (ALS)?


This progressive disease involves motoneurons of the brain stem and spinal cord, and which (in 50%) involves features of FLD with mild cognitive impairment. Authors discuss ethical issues related to ALS including a) informing the patient of the diagnosis, b) protection from unproven therapies (e.g., stem cell), c) assigning a health care power of attorney, d) benefit-risk of enrolling in therapeutic trials, e) assisted ventilation, f) end-of-life decisions, g) feeding tubes, h) the complexities of genetic testing, and i) assisted suicide. (Assisted suicide is legal only in Oregon, Washington State, Montana, Vermont, California, and under consideration by voters in Colorado in 2016).

WHAT ARE THE SPECIAL ETHICS CONSIDERATIONS IN PRION DISEASE?


Prion diseases are transmissible spongiform encephalopathies of which there are several types – sporadic Creutzfeldt-Jakob disease (sCJD), genetic prion disease (gPrD), acquired CJD, and variant CJD. Article outlines the types of prion disease, age of onset, causes, and manifestations (such as age of onset and rapidity of progression). Difficulties of diagnosis, risk of misdiagnosis, risks of transmission, lack of effective treatment, and low incidence raise unique ethical questions for patients, families, and clinicians—and special challenges for research investigations. Advocates for early identification to assure adequate scientific power. Emphasizes overlap with other neurodegenerative disorders, so research on prion disease may benefit our understanding more broadly.

“Vulnerability”

IS IT ETHICAL AND USEFUL—OR PROBLEMATIC—TO CHARACTERIZE INDIVIDUALS OR GROUPS AS “VULNERABLE”?

Common Rule. When assuring the selection of subjects is equitable, the IRB:

- “should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons” (45 CFR 46.111(3); 21 CFR 56.111).


“Vulnerable Subjects: Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy I case of refusal to participate. Examples are . . . patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent” (Glossary 1.61, p. 8).

Vulnerable Groups and Individuals (Para. 19 and 20):

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a nonvulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.


Authors “critically argue against overly generalizing assessments (‘labeling’) of vulnerability” (p. 2). CIOMS identifies several sources of vulnerability: (a) persons with limited capacity to consent/refuse, (b) subordinate members of hierarchical groups, (c) elderly persons, (d) “persons with serious, potentially disabling or life-threatening diseases, (e) “poor people, the unemployed, homeless people, refugees, nomads, some ethnic and racial minority groups, members of communities unfamiliar with modern medical concepts, individuals are politically powerless, etc.” (p. 5). Offer detailed practical guidance to protect participants (see Table 1, p. 11).

**Waivers of liability**

**IS IT LEGAL TO ASK PARTICIPANTS IN MEDICAL RESEARCH TO SIGN A WAIVER OF LIABILITY?**


This case involved a high-risk recreational sport (Himalayan mountain climbing) combined with a research project involving respiratory exercise to prevent altitude sickness. The plaintiff experienced cerebral edema. The court recognized a fiduciary relationship between investigator and subject, found medical research to be a matter of public importance (using the *Tunkl factors*), and held that a waiver of liability for negligence was against public policy (see also 45 CFR 46.116).

**See also:**

Common Rule:

“No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject’s legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence” (45 CFR 46.116; 21 CFR 50.20).


JENNIFER HORNER (ANCDS, 2016)
Cochrane Systematic Reviews of Behavioral Interventions For Neurodegenerative Disorders


“Available evidence regarding cognitive training remains limited, and the quality of the evidence needs to improve. However, there is still no indication of any significant benefit derived from cognitive training. Trial reports indicate that some gains resulting from intervention may not be captured adequately by available standardised outcome measures. The results of the single RCT of cognitive rehabilitation show promise but are preliminary in nature. Further, well-designed studies of cognitive training and cognitive rehabilitation are required to obtain more definitive evidence. Researchers should describe and classify their interventions appropriately using available terminology.” (Authors’ conclusions, p. 2).


“There is promising evidence that exercise programs may improve the ability to perform ADLs in people with dementia, although some caution is advised in interpreting these findings. The review revealed no evidence of benefit from exercise on cognition, neuropsychiatric symptoms, or depression. There was little or no evidence regarding the remaining outcomes of interest (i.e., mortality, caregiver burden, caregiver quality of life, caregiver mortality, and use of healthcare services).” (Authors’ conclusions, p. 2).


“There is evidence that telephone counselling can reduce depressive symptoms for carers of people with dementia and that telephone counselling meets important needs of the carer. This result needs to be confirmed in future studies that evaluate efficacy through robust RCTs and the experience aspect through qualitative studies with rich data.” (Authors’ conclusions, p. 2).


“Current evidence does not demonstrate any benefits or adverse effects from the use of respite care for people with dementia or their caregivers. These results should be treated with caution, however, as they may reflect the lack of high quality research in this area rather than an actual lack of benefit. Given the frequency with which respite care is advocated and provided, well-designed trials are needed in this area.” (Authors’ conclusions, p. 2).


“The delivery of FA has been incorporated within wide ranging multi-component programmes and study designs have varied according to setting - i.e. family care, care homes and hospital, with surprisingly few studies located in care homes. Our findings suggest potential beneficial effects of multi-component interventions, which utilise FA. Whilst functional analysis for challenging behaviour in dementia care shows promise, it is too early to draw conclusions about its efficacy.” (Authors’ conclusions, p. 2).

“There is insufficient evidence from randomised trials to allow any conclusion about the efficacy of validation therapy for people with dementia or cognitive impairment.” (Authors’ conclusions, p. 2).


“The methodological quality and the reporting of the included studies were too poor to draw any useful conclusions.” (Authors’ conclusions, p. 2).


“Whilst four suitable randomized controlled trials looking at reminiscence therapy for dementia were found, several were very small studies, or were of relatively low quality, and each examined different types of reminiscence work. Although there are a number of promising indications, in view of the limited number and quality of studies, the variation in types of reminiscence work reported and the variation in results between studies, the review highlights the urgent need for more and better designed trials so that more robust conclusions may be drawn.” (Authors’ conclusions, p. 2).


“We found no evidence in the available data from RCTs that aerobic physical activities, including those which successfully improve cardiorespiratory fitness, have any cognitive benefit in cognitively healthy older adults. Larger studies examining possible moderators are needed to confirm whether or not aerobic training improves cognition.” (Authors’ conclusions, p. 2).

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