

**Title**

**Unplug – Don't Drug: An alternative approach to child behavior disorder assessment and treatment**

**Running Head**

**Reviewing the impact of technology on child development and behavior**

**Abstract**

The past decade has seen an increase in personal electronic technology, with childhood TV and videogame use similarly increasing. Critical milestones for child motor and sensory development are not being met. Simultaneously there is an increasing incidence of childhood physical, psychological and behavior disorders, often accompanied by the prescription of psychotropic medication. One in six children exhibit signs of poor health, mental stress, or problems at school. Exposure to an average of eight hours per day of various forms of technologies, has resulted in a physically sedentary yet chaotically stressed existence for Canadian children. The ethical challenge for the 21st century family physician will be to move away from medication as a first line intervention for treating child behavior, and move toward treating the child's whole family, including a routine technology usage history. Technology's detrimental effects on critical milestones for child development are reviewed. This commentary by a pediatric occupational therapist outlines issues of concern for parents, family physicians, and pediatricians related to these trends, and offers a novel treatment approach: *Unplug – Don't Drug*.

**Case Review**

A seven year old boy is brought to his family physician's office by his mother at the urging of his school. In attendance is his four year old sister. Discussion with the boy's mother indicates that although his reading is at age level, this boy apparently has great difficulty producing school work, listening or paying attention in class, and is reportedly "disruptive" and "aggressive". The mother states her son has few friends, preferring instead to spend his time alone in his room watching television or playing video games. Initial assessment indicates the son appeared pale with dark circles under his eyes, slightly obese, lethargic, and non-communicative. Following a short period of questioning, the son became confrontational and combative with both the physician and his mother, abruptly leaving the physician's office and returning to the waiting room. As the mother began to apologize for her son's behavior, the physician began to take notice the boy's four year old sister, who was positioned behind the mother. When questioned regarding her daughter's health, the mother responded that the daughter frequently became upset and demonstrated high anxiety when experiencing normal every day events. The mother went on to report her daughter woke frequently in the night "screaming", was overly sensitive to noise and light, and appeared to be "hooked" on cartoons - watching up to six hours per day.

**Child Health and Academic Performance**

It wasn't all that long ago children were brought to their family physician for fractures or lacerations sustained from falling out of trees or off bicycles. Today's office visits are different. Physicians are now assessing and treating a variety of physical, psychological and behavior disorders in children that appear to be escalating at an alarming rate. One in six Canadian children have a diagnosed developmental disability (Hamilton, 2006), one in six are obese (Canadian Institutes of Health Research, 2004), and 14.3% have a diagnosed psychiatric disorder (Waddell, Hua, Garland, DeV, & McEwan, 2007). School-based occupational therapists observe increasing referrals of students to family physicians by their teachers for behavior problems, attention impairments, and learning difficulties. Child behaviors in particular present significant management difficulties for parents, teachers, and the medical community alike. Difficult child behaviors could easily be misunderstood, possibly resulting in psychiatric diagnosis and prescription of psychotropic medication (Mukaddes, Bilge, Alyanak, & Kora, 2000) and (Ruff, 2005). Between 1991 and 1995, prescriptions for psychotropic medications in the 2 – 4 year old

toddler population, as well as in children and youth tripled (Mandell, Morales, Marcus, Stahmer, Doshi, Polsky, 2008), (Zito, Safer, dosReis, Gardner, Boles, Lynch, 2000), (Zito, Safer, dosReis, Gardner, Soeken, Boles, Lynch, 2002), with 80% of this medication prescribed by family physicians and pediatricians (Goodwin, Gould, Blanco, Olfson, 2001). 28-30% of children receiving psychotropic medication are on multiple medications (Zito et al., 2003). Limited high quality evidence guiding appropriate dosing and inexperience in documentation of long term effects of these prescriptions in children may mean that these children undergo unquantified risks (dosReis, Zito, Safer, Gardner, Puccia, Owens, 2005), (Rosack, 2003), (Kirsch, Antonuccio, 2004), (Thomas, Conrad, Casler, Goodman, 2006). While some child behaviors do require extensive diagnostic procedures and possible prescription of psychotropic medication, other behaviors, especially those resulting from high technology use, require family-based interventions targeting technology reduction strategies. Understanding the critical factors for child development positions the medical profession as experts in helping families manage balance between what children need to grow and succeed with technology use.

### **Not Meeting Developmental Milestones**

Throughout most of human history, child engagement in rough and tumble outdoor play resulted in the achievement of adequate sensory and motor development required for attention and learning (Ayres, 1972), (Pelligrini, Bohn, 2005), (Tannock, 2008). Recent advances in technology have resulted in a physically sedentary child, who is also exposed to high frequency, duration and intensity of sensory stimuli, with markedly limited access to attention restorative nature (Louv, 2005). Parents now spend 40% less time with their children than they did in the 1970's (Castro, Hewlett, 1991), impacting on parent-child attachment development and socialization training. Children now immerse themselves for long durations in a virtual and often violent world, disconnecting from the world of physical play and meaningful interactions. In occupational therapy settings, children who overuse technology have described physical sensations of "body shaking", rapid heart rate and breathing, and hyper-acute vision and hearing. As these symptoms are typically associated with chronic high adrenalin states in adults, one can't help but wonder if technology overuse is creating chronic stress states in children. The three critical factors for healthy physical and psychological child development are movement, touch and connection to other humans (Insel, Young, 2001), (Korkman, 2001), (Montagu, 1972). Developing children require 3-4 hours per day of unstructured, active rough and tumble play to achieve adequate stimulation to the vestibular, proprioceptive and tactile sensory systems (National Association for Sport and Physical Education, 2002). This type of sensory input ensures normal development of core posture, bilateral coordination and optimal arousal states (Braswell, Rine, 2006). Infants with low tone, toddlers failing to reach motor milestones, and children who are unable to pay attention or achieve basic foundation skills for literacy, are now frequent visitors to pediatric physiotherapy, occupational therapy and speech and language therapy clinics.

### **Technology Usage Statistics**

North American children now average eight hours per day using a combination of non-school related technologies (television, video games, movies, internet, cell phones, iPods and other devices), with over 65% of children having televisions in their bedrooms (Rideout, Vandewater, Wartella, 2003), (Roberts, Foehr, Rideout, Brodie, 1999). Active Healthy Kids Canada gave Canadian children a grade "D" for inactivity, citing television and video games as the primary cause (Active Healthy Kids Canada 2008). 'Baby TV' now occupies 2.2 hours per day for the 0-2 year old population, and 4.5 hours per day for 3-5 year olds, and 60% of households have the television on all day (Zimmerman, Christakis, Meltzoff, 2007), as do a growing number of restaurants, cars, and even physician waiting rooms. Parents who perceive outdoor play is "unsafe" allow higher usages of technology, further limiting access to developmental components usually attained in outdoor rough and tumble play (Burdette, Whitaker, 2005).

Continuous use of technology has pervaded 21<sup>st</sup> century society, but at what cost to child health and academic performance?

### **Impact of Technology on Child Health and Academic Performance**

Technology overuse by young children is associated with developmental delays (Thakkar, Garrison, Christakis, 2006), prompting France to ban its broadcasters from airing television shows aimed at children under three years of age (CBC News, August 20, 2008). Incidence of infant “flat head” has increased 600% in the past five years, with over two thirds of physiotherapists in the United States reporting increasing incidence of infant “low tone” and subsequent failure to reach motor milestones (Jennings, 2005). Television and video game use accounts for 60% of childhood obesity, and is now considered a North American “epidemic” by physicians (Tremblay, Willms, 2005), (Strauss, Pollack, 2001). Additional studies indicate technology overuse by children may be associated with attention difficulties, poor academic achievement, and sleep impairment (Christakis, Zimmerman, 2007), (Hancox, Milne, Poulton, 2005), (Paavonen, Penonen, Roine, 2006). Christakis, Zimmerman, DiGiuseppe, and McCarty, (2004) found that each hour of television watched daily between the ages of zero and seven years equated to a 10% chance of attention problems by age seven years. While physical exercise has been repeatedly shown to significantly improve academic performance (Ratey, Hagerman, 2008). and access to “green space” significantly reduces Attention Deficit – Hyperactivity Disorder and improves attention (Faber Taylor, Kuo, Sullivan, 2001), (Kuo, Faber Taylor, 2004), schools continue to allow unrestricted technology use during recess, and are allowing playgrounds to fall into disrepair. While no one can argue the benefits of advancing technology in today’s world, many children are spending their days alone in dark rooms perfecting the “art of killing”. Desensitized to violence and lacking empathy, today’s child who overuses technology is hard wiring their brain for violence, high speed and fast-paced action, resulting in an unprecedented rise in child aggression, violence and crime (Murray et al., 2006), (Anderson et al., 2008), (Anderson, Gentile, 2007), (Buchanan, Gentile, Nelson, Walsh, Hensel, 2002). In the United States, the Academies of Physicians, Pediatricians, Psychologists and Psychiatrists have joined with the American Medical Association to classify media violence as a public health risk due to its impact on child aggression, with eventual plans to legislate the regulation of media violence by children (Anderson et al., 2003). Neural pathway formation in children who overuse technology is “short circuiting” the frontal cortex, permanently altering the way children think and behave, creating unimaginable problems for the education and penal systems (Small, Vorgan, 2008), (Ybarra, Diener-West, Markow, Leaf, Hamburger, Boxer, 2008). 25% of elementary aged children have been cyberbullied (verbally bullied online), increasing their risk of carrying a weapon to school by eight times (Kowalski, Limber, 2007), (Ybarra, Diener-West, Leaf, 2007). Young children who sextext (email nude photos using cell phones) are being arrested for distribution of child pornography (Garfinkle, 2008). These “Crimes of Technology” indicate that many children do not have the maturity or the parental guidance to use technology in a safe and responsible manner.

### **Guidelines and Recommendations**

In 2001 the American Academy of Pediatrics, Committee on Public Education released a policy statement recommending that children less than two years of age not watch any television or play any video games. In 2006 the American Academy of Pediatrics, Committee Communication further recommended that children older than two should restrict usage to one to two hours per day. Relying on parents to impose technology restrictions on their children may not be effective, as child technology usage patterns often follow that of their parents (Jordan, Hersey, McDivitt, Heitzler, 2006). Furthermore, evidence suggests some parents may have technology addictions (Horvath, 2004), as Adult Internet Addiction has been proposed for inclusion in the Diagnostic and Statistical Manual 5th Edition (Block, 2008). These conditions support consideration of a routine family technology history by primary care physicians, pediatricians, and child psychologists and psychiatrists. One option physicians may wish to consider when assessing

and treating children who overuse technology might be an initial recommendation of lessening exposure to technology, while also encouraging adequate movement, touch and human connection. Known as *Balanced Technology Management*, recommendations might follow the prescription of an “hour in equals an hour out” e.g. every hour of technology use is balanced by an hour of movement, touch and human connection. When assessing children with significant physical, psychiatric or behavior disorders that may be affecting their health or behavior, or that might limiting their ability to perform at school, physicians might consider recommending families undergo a technology “unplug”, prior to lengthy diagnostic procedures and/or use of psychotropic medication. Such a trial could require child and family undergo a one month period of *unplugging* from all forms of technology such as television, video games, movies, iPods, internet and cell phones (other than as required for school and work purposes). Current practice would suggest that unless clear safety issues are present, such a trial may be beneficial prior to prescription of psychotropic medication.

## **Conclusion**

In conclusion, evidence suggests that parents and schools allow young children extended periods of unrestricted access to various forms of technology. Further evidence suggests parents are increasingly presenting their children to physicians for assessment of complex behavior disorders that may be linked to the physical inactivity and sensory hypostimulation inherent in overuse of technology. Physician routine monitoring of technology use through application of a family technology usage history, would be a start toward achieving eventual *Balanced Technology Management*, and significantly improve the health and academic performance of children. Children with high technology usage may benefit from a one month duration technology “unplug”, prior to behavior diagnosis and prescription of psychotropic medication. Medical professionals may consider support of school-based media literacy programs, which have proven effective in reducing technology use and obesity (Robinson, 1999). Recommendations for family “disconnection” from technology, and “reconnection” with each other and nature, would go a long way toward reversing these worrisome societal trends. Trial of a TECHS NO prescription, rather than psychotropic prescription, may prove to be an effective alternative approach to child behavior disorder assessment and treatment.

## **TECHS NO Physician Prescription Pad Graphic**

Journal may wish to print accompanying TECHS NO graphic that depicts a prescription pad with the following sample of patient instructions for families. This graphic may be reproduced for inclusion within the content of this article for the International Center for Study of Psychiatry and Psychology journal.

**Technology:** 1-2 hours per day

**Exercise:** 3-4 hours per day

**Connection:** listen, hugs, bedtime stories

**Home:** no tech dinners, Sundays and holidays

**School:** no tech recess and lunch

**Nature:** explore green space

**Outdoors:** play, run, jump, breathe!

## References

- Active Healthy Kids Canada (2008). Retrieved September 14, 2009 from Active Healthy Kids Canada Website: [http://www.activehealthykids.ca/Modules/~cms.com/ecms.ashx/ExecSummary/AHK\\_ReportCard\\_ExecSummary\\_ENG.pdf](http://www.activehealthykids.ca/Modules/~cms.com/ecms.ashx/ExecSummary/AHK_ReportCard_ExecSummary_ENG.pdf).
- American Academy of Pediatrics, Committee on Communications (2006). *Children, adolescents and advertising*. *Pediatrics*, 118 (6), 2562 [PubMed](#) -2569.
- American Academy of Pediatrics, Committee on Public Education (2001). *Children, adolescents and television*. *Pediatrics*, 107 (2), [PubMed](#) 423-426.
- Anderson, C., Gentile, D., (2007). *Violent Video Game effects on Children and Adolescents*. Oxford: Oxford University Press.
- Anderson, C. A., Sakamoto, A., Gentile, D. A., Ihori, N., Shibuya, A., Yukawa, S., Naito, M., Kobayashi, H., (2008). Longitudinal Effects of Violent Video Games on Aggression in Japan and the United States. *Pediatrics*, 122 (5): e1067 [PubMed](#) -e1072.
- Anderson, C. A., Berkowitz, L., Donnerstein, E., Huesmann, L. R., Johnson, J. D., Linz, D., Malamuth, N. M., Wartella, E., (2003). The Influence of Media Violence on Youth. *Psychological Science in the Public Interest*, 4, 81-110.
- Ayres, J. A., (1972). *Sensory integration and learning disorders*. California: Western Psychological Services.
- Block, J. J., (2008). Issues for DSM – V: Internet Addiction. *Journal of Clinical Psychiatry*, 67 (5), 821 [PubMed](#) -826.
- Braswell, J., Rine, R., (2006). Evidence that vestibular hypofunction affects reading acuity in children. *International Journal of Pediatric Otorhinolaryngology*, 70 (11), 1957-1965.
- Buchanan, A. M., Gentile, D. A., Nelson, D. A., Walsh, D. A., Hensel, J., (2002). *What goes in must come out: Children's Media Violence Consumption at Home and Aggressive Behaviours at School*. Retrieved September 14, 2009 from National Institute On Media + the Family Website: [www.mediafamily.org/research/report\\_issbd\\_2002.shtml](http://www.mediafamily.org/research/report_issbd_2002.shtml).
- Burdette, H. L., Whitaker, R. C., (2005). A national study of neighborhood safety, outdoor play, television viewing, and obesity in preschool children. *Pediatrics*, 116, 657-662.
- Canadian Institutes of Health Research (evidence report dated January 12, 2004). Addressing childhood obesity: the evidence for action. Website: <http://www.cihr.ca/e/23293.html>.
- Castro, J., Hewlett, S. A., (1991, August 26). Watching a Generation Waste Away. *Time Magazine*.
- CBC News (August 20, 2008). *France pulls plug on TV shows aimed at babies*. Retrieved September 14, 2009 from CBC Website: <http://www.cbc.ca/world/story/2008/08/20/french-baby.html>.
- Christakis, D. A., Zimmerman, F. J., (2007). Violent Television During Preschool Is Associated With Antisocial Behavior During School Age. *Pediatrics*, 120, 993-999 [PubMed](#).

Christakis, D. A., Zimmerman, F. J., DiGiuseppe, D. L., McCarty, C. A., (2004). Early television exposure and subsequent attentional problems in children. *Pediatrics*, 113 (4), 708-713.

dosReis, S., Zito, J. M., Safer, D. J., Gardner, J. F., Puccia, K. B., Owens, P. L., (2005). Multiple psychotropic medication use for youths: A two-state comparison. *Journal of Child and Adolescent Psychopharmacology*, 15(1), 68 [PubMed](#) -77.

Faber Taylor, A., Kuo, F. E., Sullivan, W. C., (2001). Coping With ADD – The Surprising Connection to Green Play Settings. *Journal of Environment and Behavior*, 33(1), 54-77.

Garfinkle, S. (2008, December 10). *Sex + Texting = Sextexting*. Retrieved on September 14, 2009 from Washington Post Website: <http://voices.washingtonpost.com/parenting/2008/12/sexting.html>

Goodwin, R., Gould, M. S., Blanco, C., Olfson, M., (2001). Prescription of psychotropic medications to youth in office-based practices. *Psychiatric Services*, 52(8), 1081-1087.

Hamilton, S., (2006). Screening for developmental delay: Reliable, easy-to-use tools. *Journal of Family Practice*, 55 (5), 416-422.

Hancox, R. J., Milne, B. J., Poulton, R., (2005). Association of television during childhood with poor educational achievement. *Archives of Pediatric and Adolescent Medicine*, 159 (7), 614-618.

Horvath, C. W., (2004). Measuring television addiction. *Journal of Broadcasting and Electronic Media*, 48 (3), 378 [PubMed](#) -398.

Insel, T. R., Young, L. J., (2001). The neurobiology of attachment. *Nature Reviews Neuroscience*, 2, 129-136.

Jennings, J.T., (2005). Conveying the message about optimal infant positions. *Physical and Occupational Therapy in Pediatrics*, 25 (3), 3-18.

Jordan, A. B., Hersey, J. C., McDivitt, J. A., Heitzler, C. D., (2006). Reducing Children's Television-Viewing Time: A Qualitative Study of Parents and Their Children. *Pediatrics*, 118 (5),1303 [PubMed](#) -1310.

Kirsch, I., Antonuccio, D., (February 2004). *FDA testimony on the efficacy of antidepressants with children*. Retrieved September 14, 2009 from the Alliance for Human Research Protection Website: <http://www.ahrp.org/risks/SSRI0204/KirschAntonuccio.php>.

Korkman, M., (2001). Introduction to the special issue on normal neuropsychological development in the school-age years. *Developmental Neuropsychology*, 20 (1), 325-330.

Kowalski, R. M., Limber, S. P., (2007). Electronic Bullying Among Middle School Students. *Journal of Adolescent Health*, 41, S22-30.

Kuo, F. E., Faber Taylor, A., (2004). A Potential Natural Treatment for Attention-Deficit/Hyperactivity Disorder: Evidence from a National Study. *American Journal of Public Health*, 94(9), 1580 [PubMed](#) -1586.

Louv, R., (2005). *Last child in the woods: Saving our children from Nature-Deficit Disorder*. New York: Algonquin Books.

Mandell, D.S., Morales, K. H., Marcus, S.C., Stahmer, A. C., Doshi, J., Polsky, D. E., (2008). Psychotropic medication use among medicaid-enrolled children with Autism Spectrum Disorders. *Pediatrics*, 121 (3), 441-449.

Montagu, A., (1972). *Touching: the Human Significance of the Skin* (2<sup>nd</sup> edition). New York: Harper and Row.

Mukaddes, N. M., Bilge, S., Alyanak, B., Kora, M. E. (2000). Clinical characteristics and treatment responses in cases diagnosed as Reactive Attachment Disorder. *Child Psychiatry and Human Development*, 30 (4), 273 [PubMed](#) -287.

Murray, J., Liotti, M., Ingmundson, P., Mayberg, H., Pu, Y., Zamarripa, F., Liu, Y., Woldorff, M., Gao, J., Fox, P., (2006). Children's brain activations while viewing televised violence revealed by fMRI. *Media Psychology*, 8 (1), 25 [PubMed](#) -37.

National Association for Sport and Physical Education, (February 6, 2002). *NASPE Releases First Ever Physical Activity Guidelines for Infants and Toddlers*. Retrieved September 14, 2009 from National Association for Sport and Physical Education Website: <http://www.aahperd.org/naspe/template.cfm?template=toddlers.html>.

Paavonen, E. J., Penonen, M., Roine, M., (2006). Passive Exposure to TV Linked to Sleep Problems in Children. *Journal of Sleep Research*, 15, 154-161.

Pelligrini, A. D., Bohn, C. M., (2005). The role of recess in children's cognitive performance and school adjustment. *Educational Researcher*, 34(1), 13-19.

Ratey, J. J., Hagerman, E., (2008). *Spark: The Revolutionary New Science of Exercise and the Brain*. New York: Little, Brown and Company.

Rideout, V. J., Vandewater, E. A., Wartella, E. A., (2003). *Zero to six: electronic media in the lives of infants, toddlers and preschoolers*. Retrieved September 14, 2009 from Kaiser Family Foundation Website: <http://www.kff.org/entmedia/upload/Zero-to-Six-Electronic-Media-in-the-Lives-of-Infants-Toddlers-and-Preschoolers-PDF.pdf>.

Roberts, D. F., Foehr, U. G., Rideout, V. J., Brodie, M., (1999). *Kids and media @ the millennium: A comprehensive national analysis of children's media use*. Retrieved September 14, 2009 from Kaiser Family Foundation Website: <http://www.kff.org/entmedia/loader.cfm?url=/commonspot/security/getfile.cfm&PageID=13263>.

Robinson, T., (1999). Reducing children's television viewing to prevent obesity. *JAMA*, 282 (16), 1561-1567.

Rosack, J., (2003). Prescription data on youth raise important questions. *American Psychiatric Foundation – Clinical and Research News*, 38 (3): 1-3.

Ruff, M. E., (2005). Attention Deficit Disorder and stimulant use: An epidemic of modernity. *Clinical Pediatrics*, 44 (7), [PubMed](#) 557-563.

Small, G., Vorgan, G., (2008). *iBrain: Surviving the Technological Alteration of the Modern Mind*. New York: HarperCollins Publishing.

Strauss, R. S., Pollack, H. A., (2001). Epidemic increase in childhood overweight, 1986-1998. *JAMA*, 286 (22), 2845-2848.

Tannock, M. T., (2008). Rough and tumble play: an investigation of the perceptions of educators and young children. *Journal of Early Childhood Education*, 35, 357-361.

Thakkar, R. R., Garrison, M. M., Christakis, D. A., (2006). A systematic review for the effects of television viewing by infants and preschoolers. *Pediatrics*, 118, 2025-2031 [PubMed](#).

Thomas, C. P., Conrad, P., Casler, R., Goodman, E., (2006). Trends in the use of psychotropic medications among adolescents, 1994 to 2001. *Psychiatric Services*, 57 (1), [PubMed](#) 63-69.

Tremblay, M. S., Willms, J. D., (2005). Is the Canadian childhood obesity epidemic related to physical inactivity? *International Journal of Obesity*, 27, 1100-1105 [PubMed](#) .

Waddell, C., Hua, J. M., Garland O. M., DeV., P. R., McEwan, K., (2007). Preventing Mental Disorders in Children: A Systematic Review to Inform Policy-Making. *Canadian Journal of Public Health*, 98(3), 166 [PubMed](#) -173.

Ybarra, M. L., Diener-West, M., Leaf, P. J., (2007). Examining the Overlap in Internet Harassment and School Bullying: Implications for School Intervention. *Journal of Adolescent Health*, 41:S42-S50 [PubMed](#).

Ybarra, M. L., Diener-West, M., Markow, D., Leaf, P. J., Hamburger, M., Boxer, P., (2008). Linkages between internet and other media violence with seriously violent behavior by youth. *Pediatrics*, 122 (5), 929 [PubMed](#) -937.

Zimmerman, F. J., Christakis, D. A., Meltzoff, A. N., (2007). Television and DVD/video viewing in children younger than 2 years. *Archives of Pediatric Adolescent Medicine*, 161 (5), 473-479.

Zito, J. M., Safer, D. J., dosReis, S., Gardner, J. F., Boles, M., Lynch, F., (2000). Trends in the prescribing of psychotropic medications to preschoolers. *JAMA*, 283, 1025-1030.

Zito, J. M., Safer, D. J., dosReis, S., Gardner, J. F., Soeken, K., Boles, M., Lynch, F., (2002). Rising prevalence of antidepressants among US youth. *Pediatrics*, 109 (5), [PubMed](#) 721-727.

Zito, J. M., Safer, D. J., dosReis, S., Gardner, J. F., Magder, L., Soeken, K., Lynch, F., Riddle, M., (2003). Psychotropic practice patterns for youth. *Archives of Pediatric and Adolescent Medicine*, 157(1), 17 [PubMed](#) -25.