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Alcohol, tobacco and prescription drugs: The relationship with illicit drugs in the treatment of substance users.

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Abstract

Alcohol, tobacco, prescription drug and illicit drug use frequently co-occur. This paper reviews the extent of this co-occurrence in both general population samples and clinical samples, and its impact on treatment outcome. We argue that the research base for understanding comorbidity between tobacco, alcohol, prescription and illicit drugs needs to be broadened. We specifically advocate for: 1) more epidemiological studies of relationships between alcohol, tobacco and other illicit drug use; and 2) increased research on treatment options that address the problematic use of all of these drugs.

Keywords: Comorbidity; Alcohol Use Disorder; Substance Use Disorder; Treatment Outcome

Abbreviations: NCS, National Comorbidity Survey; NCS-R, National Comorbidity Survey Replication; NESARC, National Epidemiological Survey in Alcohol and Related Conditions; NSMHWB, The National Survey on Mental Health and Well-being, Australia; SUD, Substance Use Disorder

Introduction

In the addictions field, different types of substance use often co-occur and so do different substance use disorders. This co-occurrence of disorder is often referred to as homotypic comorbidity (Darke, et al., 2009; Degenhardt, Hall, and Lynskey, 2001). Comorbid substance use disorders may occur *concurrently* and *successively*. Concurrent comorbidity occurs when two or more disorders are present at the same time (Hall, Degenhardt, and Teesson, 2009), such as, heroin dependence and alcohol dependence. Successive comorbidity occurs when disorders occur at different times in a person's life, in ways that may or may not be causally related to each other (Hall, et al., 2009). For example, if a heroin dependent person ceases using heroin but subsequently develops alcohol dependence. The complexity of patterns of comorbidity between substance use disorders remains a significant challenge to clinicians and researchers. In this paper we have focussed on comorbidity of substance use disorders (American Psychiatric Association, 2000; World Health Organization, 1993) as these are generally the focus of treatment services.

Our understanding of the extent of comorbidity between alcohol, tobacco and prescription drugs and illicit drugs is driven by two sources, studies of specialist treatment samples and epidemiological surveys of representative samples of the population. As illicit drug use is often hidden and not well represented at population levels, both studies are critical for our understanding of comorbidity and its consequences. Clinical studies provide evidence on low prevalence forms of drug dependence and epidemiological studies are needed to obtain a more accurate picture of patterns of comorbidity that are unaffected by treatment seeking.

What have Population Studies shown?

Homotypic Comorbidity: Population Studies

The most comprehensive epidemiological data on patterns of *homotypic* comorbidity comes from surveys in the USA such as the National Comorbidity Survey (NCS) in the early 1990s (Kessler, et al., 1994) and the National Comorbidity Survey-Replication (NCS-R) in 2001-2003 (Kessler, et al., 2004; Kessler, Chiu, Demler, and Walters, 2005) and the large National Epidemiological Survey in Alcohol and Related Conditions (NESARC) (Compton, Thomas, Stinson, and Grant, 2007; Grant, et al.,

2004; Hasin, Stinson, Ogburn, and Grant, 2007). Similar studies have also been conducted in other developed countries including Australia (The National Survey of Mental Health and Well-being; NSMHWB 1997 & 2007) (Andrews, Hall, Teesson, and Henderson, 1999; Andrews, Henderson, and Hall, 2001; Teesson, et al., in press; Teesson, Slade, and Mills, 2009), Germany (John, Meyer, Rumpf, and Hapke, 2004), and the United Kingdom (Farrell, et al., 2001; Jenkins, et al., 1997) (Table 1).

These studies have revealed that comorbidity between alcohol, tobacco, prescription drug use disorder and illicit substance use disorders is consistently high (SUDs) (Degenhardt, et al., 2001; Kessler and Wang, 2008). For example, population studies have shown that among those diagnosed with an alcohol use disorder the odds of having a cannabis use disorder is 10.5 (Burns and Teesson, 2002) and 36.3 for a cocaine use disorder (Regier, et al., 1990). Those with cannabis use disorder are 19.3 times more likely to be alcohol dependent (Degenhardt and Hall, 2003) and 5.0 times more likely to be tobacco smokers (Degenhardt and Hall, 2001).

Co-morbidity

Table 1
Recent general population studies examining comorbidity (since 1990)

Study	Year administered	Country	Total (N)	Instruments used
Kessler et al. (1994)	1990-1992	United States	8,098	• Composite International Diagnostic Interview (CIDI) (World Health Organization, 1990)
Jenkins et al. (1997)	1993	Great Britain	10,108	• Clinical Interview Schedule - Revised (CIS-R) (Lewis, Pelosi, Araya, and Dunn, 1992)
John, Meyer, Rumpf, and Hapke (2004)	1996-1997	Germany	4,075	• Munich-Composite International Diagnostic Interview (M-CIDI) (Wittchen, et al., 1995)
Andrews, Hall, Teesson, and Henderson (1999)	1997	Australia	10,641	• Composite International Diagnostic Interview Version 2.1 (CIDI-2.1) (Andrews and Peters, 1998) • Mini-Mental State Examination (MMSE)(Folstein, Folstein, and McHugh, 1975) • 12-item Short Form Health Survey (SF-12)(Ware, Kosinski, and Keller, 1996)
Grant et al. (2004)	2001-2002	United States	43,093	• Alcohol Use Disorder and Associated Disabilities Interview Schedule– DSM-IV Version (AUDADIS-IV) (Grant, Dawson, and Hasin, 2001)
Kessler et al. (2004)	2001-2003	United States	9,282	• The World Mental Health survey initiative version of the World Health Organization Composite International Diagnostic Interview (WMH-CIDI) (Kessler and Ustun, 2004)
Slade et al. (2009)	2007	Australia	8,841	• The World Mental Health survey initiative version of the World Health Organization Composite International Diagnostic Interview (WMH-CIDI) (Kessler and Ustun, 2004)

What have Clinical Studies shown?

Clinical studies have demonstrated high rates of co-morbidity between licit and illicit drug use disorders. For example, of those with a heroin use disorder, 26% have lifetime benzodiazepine dependence and 23% of those with benzodiazepine dependence have a lifetime cocaine dependence (Ross and Darke, 2000). Among those with an alcohol use disorder 20-30% have a lifetime cocaine dependence (Miller, 1991), while those with a cocaine dependence have 57-88% chance of having a lifetime alcohol use disorder (Higgins, Budney, Bickel, and Foerg, 1994; Wiseman and McMillan, 1996). High rates of tobacco smoking have also been found among drug dependent persons in clinical settings. For example, of those with a cocaine use disorder 78% currently smoked tobacco (Roll, Higgins, Budney, Bickel, and Badger, 1996). Current tobacco smoking has been shown to range from 43-70% among those with a cannabis use disorder (Copeland, Swift, and Rees, 2001; Moore and Budney, 2001) and to be as high as 96% among those with a heroin dependence (Ross, et al., 2005).

Understanding Comorbidity

There are a number of hypotheses that may explain the comorbidity between substance use disorders (Agrawal and Lynskey, 2009). Each has different implications for treatment and prevention.

First, licit drug use may increase the risk of illicit drug use. Kandel (1975) suggested that illicit drug users go through a sequential progression of drug use, with the use of licit substances preceding and increasing the risk of using illicit drugs.

The high association between tobacco and illicit drug use provides preliminary support for this argument, with studies showing that tobacco smokers are more likely to use cannabis, cocaine and heroin than non-smokers (Lai, Lai, Page, and McCoy, 2000; Lewinsohn, Rohde, and Brown, 1999). Hypotheses about the nature of the relationships between alcohol, tobacco, prescription drugs and illicit drugs are indeed complex and this hypothesis does not cover all relationships and complexities.

A second possibility is that illicit drug use may indirectly increase the risk of licit drug use. Results obtained from a sample of students at the University of Florida suggested tobacco smoking often follows or coincides with the onset of marijuana use (Tullis, Dupont, Frost-Pineda, and Gold, 2003). Similarly, while benzodiazepine use is common among heroin users, its onset often follows that of heroin, in some cases commencing up to an average of 3 to 6 years later (Navaratnam and Foong, 1990).

A third possibility is that co-morbidity between substance use disorders arises from common causes. The syndrome of delinquency, alcohol and drug abuse, precocious sexual activity, and poor school performance may, for example, be manifestations of a shared genetic predisposition and family circumstances that increase the chances of developing alcohol and drug dependence disorders (Grant, et al., 2006; Jessor and Jessor, 1977; Reinherz, Giaconia, Hauf, Wasserman, and Paradis, 2000). Associations between conduct disorder, alcohol and cannabis dependence have been attributed to shared environmental influences common to all three sets of symptoms (Tsuang, Bar, Harley, and Lyons, 2001), such as deviant parental behaviour and a pathological home environment that increases exposure to alcohol and cannabis abuse (Lytton, 1990; Rutter, 1994; Young, et al., 1995).

Children with conduct disorder are more likely to start using alcohol and other drugs earlier than their peers because of their greater propensity to take risks. Earlier initiation results in a longer history of “heavier” alcohol and other drug use, increasing the risks of developing alcohol and drug dependence at an early age (Cerda, Sagdeo, and Galea, 2008; Fergusson and Horwood, 1997; Hall, et al., 2009).

Prospective epidemiological studies

Hypotheses about the nature of the relationships between alcohol, tobacco, prescription drugs and illicit drugs cannot be clearly distinguished in cross-sectional epidemiological studies that use retrospective life histories to assess temporal and causal relationships between disorders. More direct tests require longitudinal studies (e.g., Coffey, Lynskey, Wolfe, and Patton, 2000; Grant, et al., 2006) of representative population samples to minimise the selection bias that affects treatment samples. To date a limited number of such studies have been carried out. It is difficult to do this as

illicit drug use is so hidden due to the social and legal consequences of illicit drug use. Their results suggest that causal relationships can operate in both directions between substance use disorders, for example, tobacco can increase the likelihood of persistent cannabis use (Coffey, et al., 2000) and cannabis use can increase the likelihood of nicotine dependence (Patton, Coffey, Carlin, Sawyer, and Lynskey, 2005; Timberlake, et al., 2007).

For example, Patton et al. (2005) studied the association between cannabis use and tobacco use in a prospective study of 1,943 young Australians from the age of 14 to 21 years. In this well conducted study, the authors found associations between non-tobacco-smoking teens and young adults who reported weekly or greater cannabis use and increased risk of late initiation of tobacco use and the development of nicotine dependence. In detail, they found that young non-tobacco-smoking teens who reported weekly cannabis use at least once had an eightfold increase in the odds of later initiation of tobacco use. Among those at 21 years who were not yet nicotine dependent, daily cannabis use raised the odds of nicotine dependence threefold by the age of 24 years. This relationship remained after controlling for current tobacco use patterns.

Large scale longitudinal studies of epidemiologically defined cohorts of adults are needed to examine relationships between comorbid disorders. The recent 3 year follow up of incident disorders in the NESARC cohort and their relationship to baseline disorders provides a good illustration of the potential value of this approach (Grant, et al., 2009). In this study, 34 653 persons who were interviewed in the first wave of the NESARC study were followed up after 36 months and reassessed for symptoms of a wide range of common mental and substance use disorders. The sample size was significant and large enough to examine relationships between demographic characteristics and substance use at the baseline assessment and incident disorders during the 3 year follow up period. The disorders with the highest incidence rates (per 100 person years) were: alcohol dependence (1.7); alcohol abuse (1.0); major depressive disorder (1.5); and generalised anxiety disorder (1.1). The demographic predictors of these disorders were consistent with previous research: alcohol and drug use disorders were more common among young males; and major depressive disorder was more common among young females (Grant, et al., 2009).

The presence of mental disorders at baseline predicted incident disorders during the 3 year follow up (after controlling for demographic variables). Alcohol abuse and dependence were strong predictors of each other, as were drug abuse and drug dependence. These findings emphasise the strong relationships between these disorders in population studies (Grant, et al., 2009).

While longitudinal epidemiological studies provide suggestions of causation the evidence will be required from a number of sources. The Bradford Hill (Hill, 1966) criteria provide a framework for the accumulation of this evidence and have been used to examine causal relationships between cannabis and psychosis (Hall, Degenhardt, and Teesson, 2004). Such reviews, to our knowledge have not been undertaken in examining the relationship between alcohol, tobacco, or prescription drugs with illicit drugs.

The contribution of twin and genetic epidemiological studies

The role of shared genetic and environmental risk to common patterns of comorbidity can be examined most effectively in twin studies (Kendler and Prescott, 2006). Rates of disorders can be compared in identical and fraternal twins who are discordant for either risk exposures or specific disorders. The association between cannabis and other illicit drug use has been tested in this way. Lynskey et al. (2003) tested the hypothesis that the association between cannabis and other illicit drug use is explained by shared genes and environment. The relationship between cannabis and other illicit drug use was examined in 311 monozygotic (136) and dizygotic (175) twin pairs in which one twin had and the other twin had not used cannabis before the age of 17 years. The argument was that if the association was attributable to a shared environment then discordant twins raised together should not differ in the use of other illicit drugs. Similarly, if the association was attributable to shared genetic vulnerability to drug dependence then there should be no difference in the use of other illicit drugs between monozygotic twins who did and did not use cannabis before age 17. The authors found that the twin who had used cannabis before age 17 was more likely to have used other illicit drugs than their co-twin who had not. More studies of this kind can add to our knowledge of the influences on the common patterns of comorbidity.

Why does Comorbidity across Substance Use Disorders matter?

Comorbidity across substance use disorders matters for both our understanding of disorders and our treatment response. Understanding why different drug use disorders co-occur may provide important clues to the aetiology of these disorders. A better understanding of these comorbidities may also help to inform treatment practices. At present the presenting problem is often the sole focus of care and additional comorbidities and their impact on care are frequently ignored or considered too complex to warrant response (Teesson, et al., 2008; Williamson, Darke, Ross, and Teesson, 2006).

Secondly, individuals diagnosed with comorbid drug use disorders often have a poorer treatment response and a worse course of illness over time (Darke, et al., 2009; Flannery, Morgenstern, McKay, Wechsberg, and Litten, 2004; Gossop, Marsden, Stewart, and Rolfe, 2000; Kessler, 1995; Kessler and Wang, 2008; Williamson, et al., 2006).

This is probably in part because comorbid disorders are not diagnosed and treated and in part because persons with more than one disorder are more difficult to treat (Hall, et al., 2009). It is also clear that we require a better understanding of the processes of treatment (Magura, 2000). Comorbidity therefore has important implications for treatment. For example, cocaine use has been shown to be an independent predictor of poorer outcomes among persons treated for heroin dependence (Williamson, et al., 2006). Whether such comorbidity indicates a more severe problem, leads to a different response to treatment in general, or predicts different responses to particular treatments is not yet known.

What impact does Alcohol, Tobacco and Prescription Drug Use have on the Treatment of Illicit Drug Use?

Alcohol use disorders that are comorbid with illicit drug use has been associated with a more severe disorder and to also complicate intervention efforts. Clinical research has found relationships between high rates of alcohol use and both shorter treatment retention rates, and increased risk of relapse (McKay, Alterman, Rutherford, Cacciola, and McLellan, 1999; Mengis, Maude-Griffin, Delucchi, and Hall, 2002; Simpson, et al., 1997; Stenbacka, Beck, Leifman, Romelsj, and Helander, 2007). It is not yet

known if comorbidity is a marker for more severe disorders or leads to a slower response to treatment. In addition, NTORS, a large naturalistic study of persons treated for drug use-related problems in the United Kingdom, found a heightened mortality and overdose risk among those who had high levels of alcohol consumption (Gossop, et al., 2000). Schmitz et al. (1997) compared the treatment outcomes for a 12 week CBT trial among cocaine dependent individuals with and without alcohol dependence. At the end of treatment, while both groups reported using significantly less alcohol and cocaine use, and overall improvement on addiction severity and psychiatric symptomatology, was poorer in those who were also alcohol dependent (Schmitz, et al., 1997)

The Australian Treatment Outcome Study (ATOS) has shown that benzodiazepine use among heroin dependent clients is related to poorer psychological and physical health (Darke, et al., 2009). Benzodiazepine use has also been associated with poorer retention rates (Schiff, Levit, and Moreno, 2007) and greater likelihood of using heroin and cannabis (Bleich, Gelkopf, Weizman, and Adelson, 2002).

The effectiveness of tobacco dependence interventions and smoking cessation efforts with substance users in treatment has been explored in a number of studies (e.g., Burling, Burling, and Latini, 2001; Campbell, Wander, Stark, and Holbert, 1995; Gariti, et al., 2002; Shoptaw, et al., 2002; Story and Stark, 1991). In general, successful smoking cessation appears to have a positive impact on long-term abstinence (Prochaska, in press). Behavioral antismoking interventions have shown promise among cocaine dependent outpatients (Wiseman, Williams, and McMillan, 2005). A limited number of studies have also explored the impact of tobacco cessation interventions among individuals maintained on methadone (e.g., Shoptaw, et al., 2002; Stein, et al., 2006). Results have not found that either behavioural interventions or nicotine patches increase quit rates at follow up (Stein, et al., 2006).

What impact does Illicit Drug Use have on the Treatment Outcomes for Alcohol, Tobacco and Prescription Drug Use?

There is a clear trend in the alcohol, tobacco and prescription drug dependence literature to exclude individuals with comorbid illicit drug use from clinical treatment trials. For example, illicit drug users were excluded from both the large Combined

Pharmacotherapies and Behavioral Interventions (COMBINE) trial for alcohol dependence (Anton, et al., 2006), and Project MATCH (Project MATCH Research Group, 1997; 1998). Those dependent on illicit drugs were also excluded from The Collaborative European Anti-Smoking Evaluation (CEASE) multicentre trial that evaluated the effects of nicotine patches through a randomised, double-blind placebo controlled smoking cessation study (Tonnesen, et al., 1999). This practice ignores the high rates of comorbidity and denies these patients access to more effective treatment for their alcohol, tobacco and prescription drug use-related problems.

Some studies have explored the effectiveness of treatment on patients concurrently dependent on cocaine and alcohol. Naltrexone has also been shown to be an efficacious treatment for alcohol dependence (Garbutt, et al., 2005) but leads to more mixed results when used to treat individuals with co-occurring cocaine and alcohol abuse or dependence (Hersh, Van Kirk, and Kranzler, 1998; Oslin, et al., 1999; Schmitz, Stotts, Sayre, DeLaune, and Grabowski, 2004). In an open trial in individuals with co-occurring alcohol and cocaine dependence, Naltrexone reduced reported use of both drugs (Hersh, et al., 1998). However, when Naltrexone was compared with placebo in a controlled trial among individuals with co-morbid alcohol and cocaine use, consumption of cocaine and alcohol was equally reduced in both groups, that is, there was no advantage of Naltrexone over the placebo treatment (Oslin, et al., 1999).

Disulfiram has also shown promising results for individuals diagnosed with either cocaine (George, et al., 2000; Petrakis, et al., 2000) or alcohol dependence (De Sousa and De Sousa, 2005). In individuals with co-occurring cocaine and alcohol dependence, however, it only decreased cocaine use in the long term (Carroll, et al., 2004). Naltrexone and Disulfiram in combination, appear to be superior to either drug alone or to placebo in producing higher rates of abstinence to both cocaine and alcohol (Pettinati, et al., 2008). It has also been shown in a 12 week outpatient study of patients “abusing” both cocaine and alcohol that the combination of either Disulfiram or Naltrexone with cognitive behaviour therapy produced larger reductions in both alcohol and cocaine use than cognitive behaviour therapy alone (Grassi, Cioce, Guidici, Antonilli, and Nencini, 2007).

Conclusions

The central foci of research to date has been on large scale epidemiological studies of the prevalence and correlates of comorbidity in the general population and small scale studies among clinical populations. The epidemiological research has provided important information on patterns of comorbidity that are unaffected by referral biases that affect treatment samples (Berkson, 1947). There are still very few treatment outcome studies of patients diagnosed with comorbid alcohol, tobacco and illicit drug use-related problems.

We need to broaden the research base if we are to better understand the reasons for the common patterns of comorbidity that will enable us to more effectively treat persons with comorbid disorders and more speculatively, to prevent these disorders from occurring. This research should include: prospective studies of relationships between alcohol and other drug use disorders; discordant twin studies; and better evaluations of the effectiveness of treatment programs for the most common patterns of comorbidity.

THE AUTHORS

Prof Maree Teesson

Prof Teesson is Acting Director at the National Drug and Alcohol Research Centre and NHMRC Research Fellow. The National Drug and Alcohol Research Centre is Australia's largest drug and alcohol research centre and has over 150 academic, research and administrative staff and an international reputation for drug and alcohol research.

Prof Teesson has made a major contribution to Australia's health and medical research effort in the field of mental health and drug and alcohol. In particular, she is known nationally and internationally for her research on the comorbidity between mental disorders and drug and alcohol disorders. Prof Teesson has also been a key contributor in developing new approaches to the measurement and treatment of drug and alcohol problems and the evaluation of health service delivery.

Prof Teesson has a strong track record of winning competitive scientific grant funding and has published more than 140 peer reviewed papers, reports and books. In addition to her position at NDARC, Prof Teesson a prestigious Research Fellowship from

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Ms Farrugia has been working as a research officer with the National Drug and Alcohol Research Centre, University of NSW, since October 2008. She is currently working as part of a team, co-ordinated by Dr Katherine Mills, looking at the integrated treatment of post traumatic stress disorder and substance use. Ms Farrugia completed a Bachelor of Psychology honours degree at Macquarie University in 2008 and has been volunteering as a telephone counsellor with Lifeline Australia since 2007.

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Dr Mills is a Senior Lecturer and National Health and Medical Research Council Research Fellow at the National Drug and Alcohol Research Centre, University of NSW. Her research focuses on the epidemiology and treatment of co-occurring substance use and mental health disorders, in particular, post traumatic stress disorder. Dr Mills has published widely in the area, and the importance of her research has been recognised by awards from the Australasian Society for Traumatic Stress Studies (2004), the Australasian Professional Society for Alcohol and Other Drugs (2007), and the US College on Problems of Drug Dependence (2009).

Prof Wayne Hall

Prof Hall is an NHMRC Australia Fellow in addiction neuroethics at the University of Queensland Centre for Clinical Research. He was formerly: Professor of Public Health Policy in the School of Population Health (2005-2010) and Director of the Office of Public Policy and Ethics at the Institute for Molecular Bioscience (2001-2005) at the University of Queensland; and Director of the National Drug and Alcohol Research Centre at UNSW (1994-2001). He has advised the World Health Organization on: the health effects of cannabis use; the effectiveness of drug substitution treatment; the scientific quality of the Swiss heroin trials; the contribution

of illicit drug use to the global burden of disease; and the ethical implications of genetic and neuroscience research on addiction.. In 2001 he was identified by the Institute for Scientific Analysis as one of the world's most highly cited social scientists in the past 20 years. He was awarded an NHMRC Australia Fellowship in 2009 to research the public health, social policy and ethical implications of genetic and neuroscience research on drug use and addiction.

Dr Andrew Baillie

Dr Baillie is a Senior Lecturer and Director of Postgraduate Clinical Training at Macquarie University. Over the past years he has been funded for two areas of research – the treatment of comorbid mental disorders (NHMRC and NSW Health Department), the empirical examination of psychiatric diagnostic criteria using psychometrics and epidemiological datasets (NHMRC). Dr Baillie has also been collaborating in an Australian Teaching and Learning Council Grant for curriculum renewal in clinical psychology training with A/Prof Nancy Pachana, Dr Kate Sofronoff and others at the University of Queensland and at other Australian Universities.

Dr Baillie is a registered clinical psychologist and is a member of the Clinical College of the Australian Psychological Society, with an honorary appointment as a clinical psychologist in the Drug Health Services at Royal Prince Alfred Hospital in Sydney.

Glossary

Co morbidity: the presence of at least one additional disorder (Burns, Teesson, and O'Neill, 2005)

Homotypic co morbidity: the co-occurrence of disorders within a diagnostic grouping (Angold, Costello, and Erkanli, 2003)

Concurrent co morbidity: when two or more disorders are present at the same time (Hall, et al., 2009)

Successive co morbidity: when disorders occur at different times in a person's life, in ways that may or may not be causally related to each other (Hall, et al., 2009)

Prospective research: variables are measured through direct recording in the present (Portney and Watkins, 2000)

Retrospective research: the examination of data that have been collected in the past (Portney and Watkins, 2000)

Longitudinal study: the researcher follows a cohort of subjects over time, performing repeated measurements at prescribed intervals (Portney and Watkins, 2000)

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